

REARRANGEMENTS OF STEROIDS

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ABSTRACT

The reactions of 4 $\alpha$ -acetoxy-5 $\alpha$ - hydroxy- and acetoxy- cholestanes and 4 $\beta$ -acetoxy-5 $\beta$ - hydroxy- and acetoxy- cholestanes with  $\text{H}_2\text{SO}_4\text{-Ac}_2\text{O-AcOH}$  and  $\text{BF}_3\cdot\text{Et}_2\text{O-Ac}_2\text{O}$  respectively have been investigated. The course of the reactions has been found to be dependent on the orientation of the C(4) and C(5) substituents.

A study of the rearrangements of 3 $\beta$ ,6 $\beta$ -diacetoxy-5 $\alpha$ -cholestan-5-ol (5b) and 4 $\beta$ -acetoxy-5 $\beta$ -cholestan-5-ol (26b) with  $\text{D}_2\text{SO}_4\text{-DOAc-Ac}_2\text{O}$  gave rearranged products which contain no deuterium. This contrasts with previous suggestions that olefins and cyclopropanes are intermediates in backbone rearrangements.

The effects of electron withdrawing substituents in rings A, B, and D have been investigated in the reactions of 5 $\alpha$ - hydroxy- and acetoxy- cholestanes with  $\text{H}_2\text{SO}_4\text{-Ac}_2\text{O-AcOH}$  and  $\text{BF}_3\cdot\text{etherate-Ac}_2\text{O}$  respectively, and 3 $\beta$ ,5 $\alpha$ ,6 $\beta$ -triacetoxyandrostan-17-one (72b) with  $\text{BF}_3\cdot\text{etherate-Ac}_2\text{O}$ .

An unsuccessful attempt to synthesise 9 $\beta$ -cholest-4-ene (87) and 10 $\alpha$ -cholest-4-ene (86) is reported.

The reactions of 3 $\beta$ -acetoxy- and hydroxy- 9 $\beta$ -cholest-5,7-dienes (85) and 3 $\beta$ -acetoxy- and benzoyloxy- 10 $\alpha$ -cholest-5,7-dienes (83) with tetracyanoethylene (TCNE), maleic anhydride and 4-phenyl-1,2,4-triazoline-3,5-dione have been investigated. A 5 $\alpha$ ,8 $\alpha$ -cycloadduct has been formed between TCNE and 3 $\beta$ -benzoyl-10 $\alpha$ -cholest-5,7-diene the only known example of such a ring B cycloadduct.

## INTRODUCTION

Skeletal rearrangements in steroids and terpenoids involving hydride and methyl shifts have been the subject of an extensive literature. Reaction of friedel-3-ene (1) with HCl<sup>1,2</sup> to give olean-13(18)-ene (2) and 18 $\alpha$ -olean-12-ene (3) is a particularly interesting example of a molecular rearrangement involving many atoms. This rearrangement was considered by Courtney *et al.*<sup>3</sup> to involve a stepwise mechanism<sup>4</sup> with protonation of the 3-olefinic bond being the first step in the reaction. This was followed by migration of the 5 $\beta$ -methyl group to C(4) with subsequent loss of the 10 $\alpha$ -hydrogen to give glutin-5(10)-ene (4). This product reacted further with HCl to give olean-13(18)-ene (2) formed by protonation of the 5(10)-olefinic bond followed by migration of three methyl groups and one hydrogen<sup>5</sup> (Scheme 1). The rearrangement is terminated by loss of the 18 $\beta$ -hydrogen.

18 $\alpha$ -Olean-12-ene (3) is formed by protonation of the 13(18)-olefinic bond of olean-13(18)-ene (2) followed by loss of a C(12)-hydrogen (Scheme 1). The unfavourable interaction between the 13 $\alpha$ - and 20 $\alpha$ -methyl groups in friedel-3-ene (1) and glutin-5(10)-ene is relieved in the formation of olean-13(18)-ene (2) and 18 $\alpha$ -olean-12-ene (3) (Figure 1). Relief of this interaction has been suggested to be the driving force of the rearrangement<sup>6</sup>.

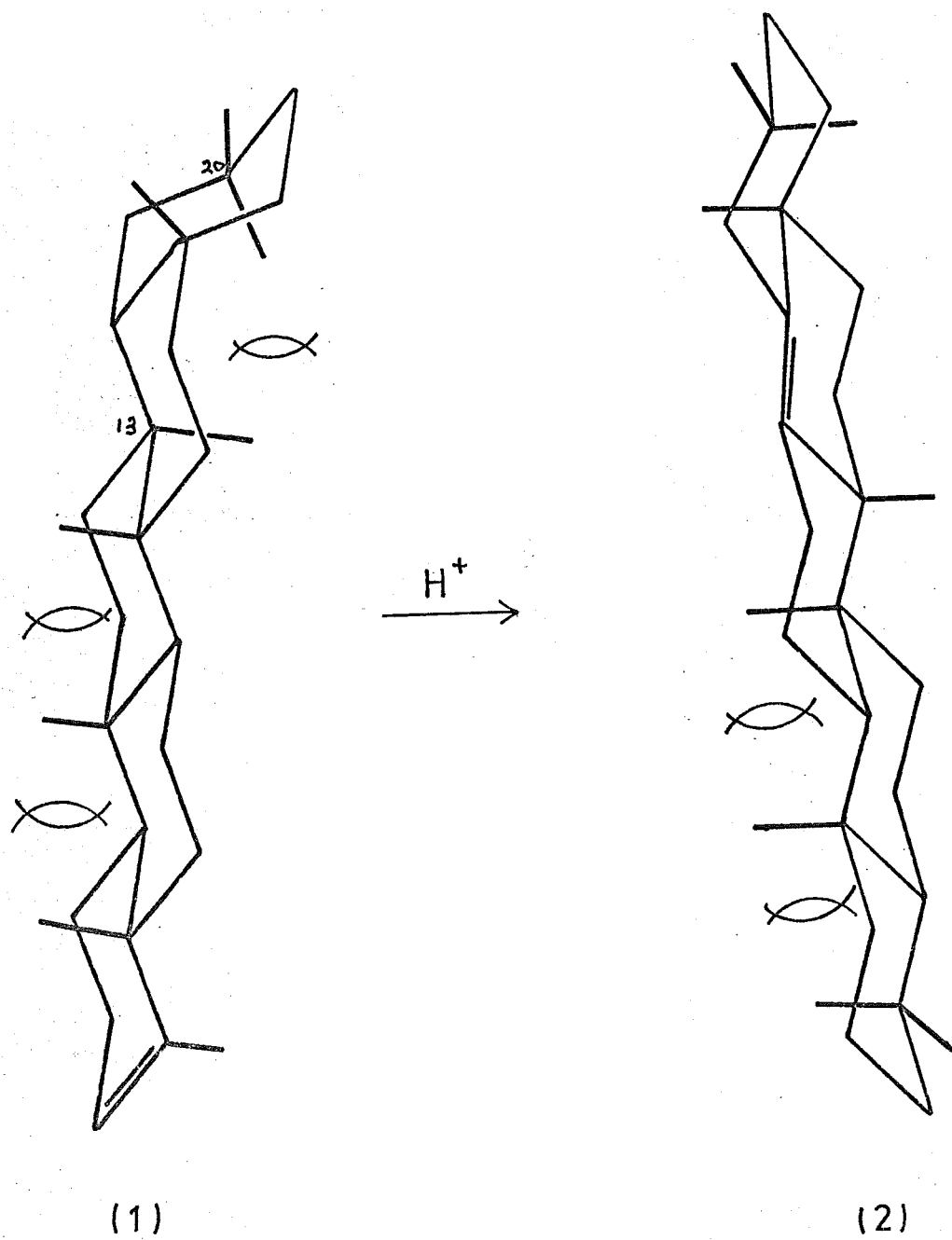
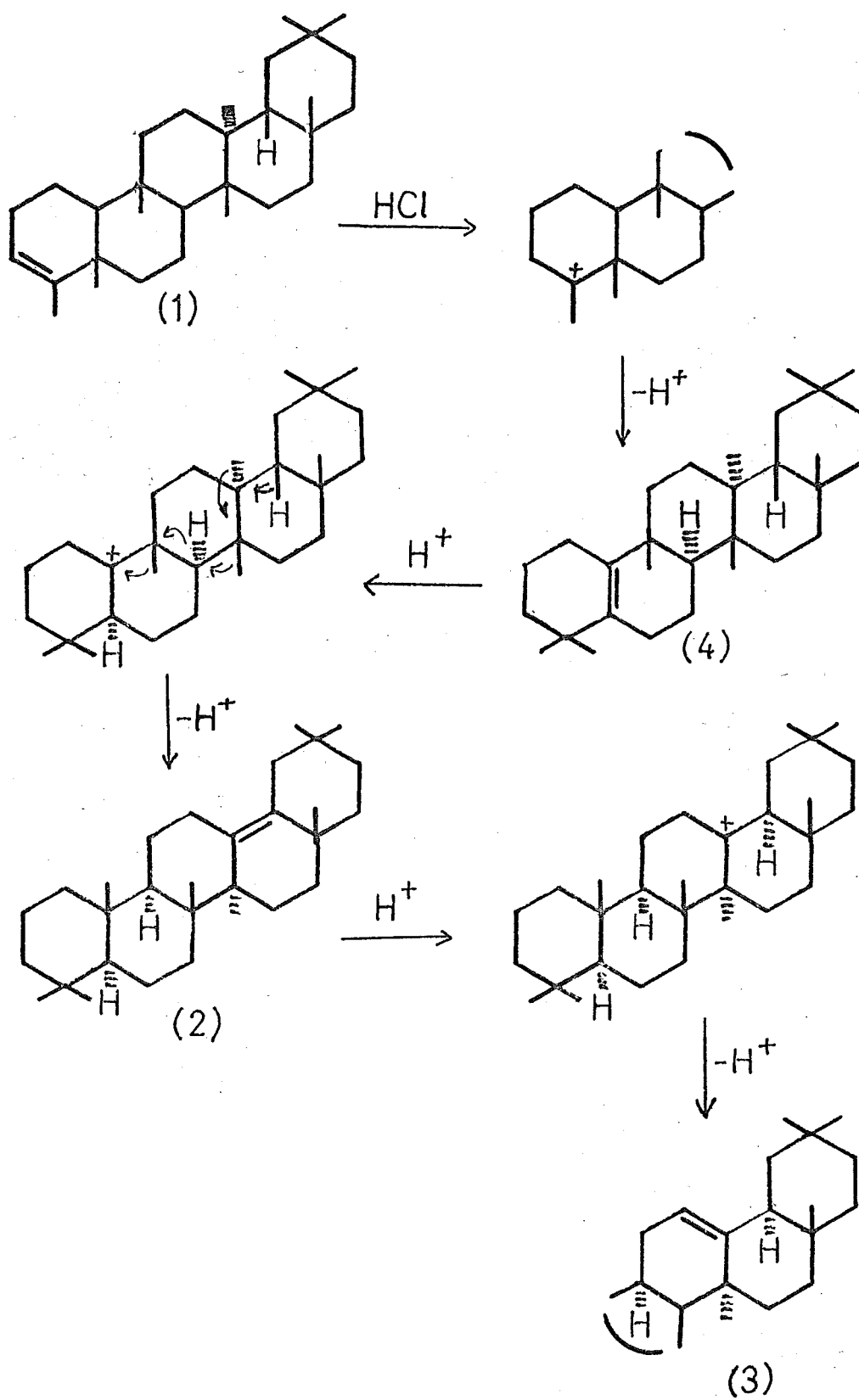


Figure 1

[ " ⋈ " Indicates steric compression. ]

Scheme 1. Rearrangement of Friedel-3-ene with Acid



Analogous "backbone" or "spinal" rearrangements have been observed in the steroid nucleus. Reactions of  $3\beta,6\beta$ -diacetoxy- $5\alpha$ -hydroxy-steroids (5) with either sulphuric acid or potassium hydrogen sulphate in acetic acid and acetic anhydride result in the formation in high yield, of  $3\beta,6\beta$ -diacetoxy- $5\beta$ -methyl-19-nor-9(10)-olefins (6)<sup>8-15</sup>. This rearrangement involved migration of the  $10\beta$ -methyl group to the  $5\beta$ -position with loss of  $9\alpha$ -hydrogen and is known as the "Westphalen" rearrangement. Kinetic measurements on a series of  $6\beta$ -substituted- $3\beta$ -acetoxy- $5\alpha$ -cholestan-5-ols in  $\text{H}_2\text{SO}_4\text{-Ac}_2\text{O-AcOH}$  gave a Taft  $\rho^*$  value of -4.8, consistent with the development of an electron deficient centre at C(5) in the rate determining step<sup>18,19</sup>.

The more extensively rearranged product,  $3\beta,6\beta$ -diacetoxy- $5\beta,14\beta$ -dimethyl-18,19-bisnorcholest-13(17)-ene (7) was obtained from the reaction of  $3\beta,5\alpha,6\beta$ -triacetate (5e) with  $\text{BF}_3$ .etherate in acetic anhydride.<sup>16,17</sup> This compound was also obtained, but in low yield, from the reaction of  $3\beta,6\beta$ -diacetoxy- $5\alpha$ -cholestan-5-ol (5a) with  $\text{H}_2\text{SO}_4\text{-Ac}_2\text{O-AcOH}$ .<sup>12</sup>

The energy requirement for a fully concerted backbone rearrangement involving many groups would be prohibitively high. Hendrikson<sup>20</sup> calculated that the energy difference between the chair and a half chair conformation of cyclohexane is ca  $60 \text{ kJ.mole}^{-1}$ . For rearrangement of friedel-3-ene (1) to olean-13(18)-ene (2), four methyl groups and two hydrogen atoms migrate. For the rearrangement to be concerted four rings of the molecule would need to flatten synchronously from chair to half-chair conformations. It is probable that the energy for a fully concerted backbone rearrangement would therefore be ca  $360 \text{ kJ.mole}^{-1}$ <sup>21</sup>. Two reasonable mechanisms have been postulated

for the backbone rearrangement of steroids and terpenoids. The first involves a series of equilibrating olefinic intermediates (Scheme 2) and the second, a series of rapidly interconverting carbonium ion intermediates <sup>22</sup> (Scheme 3).

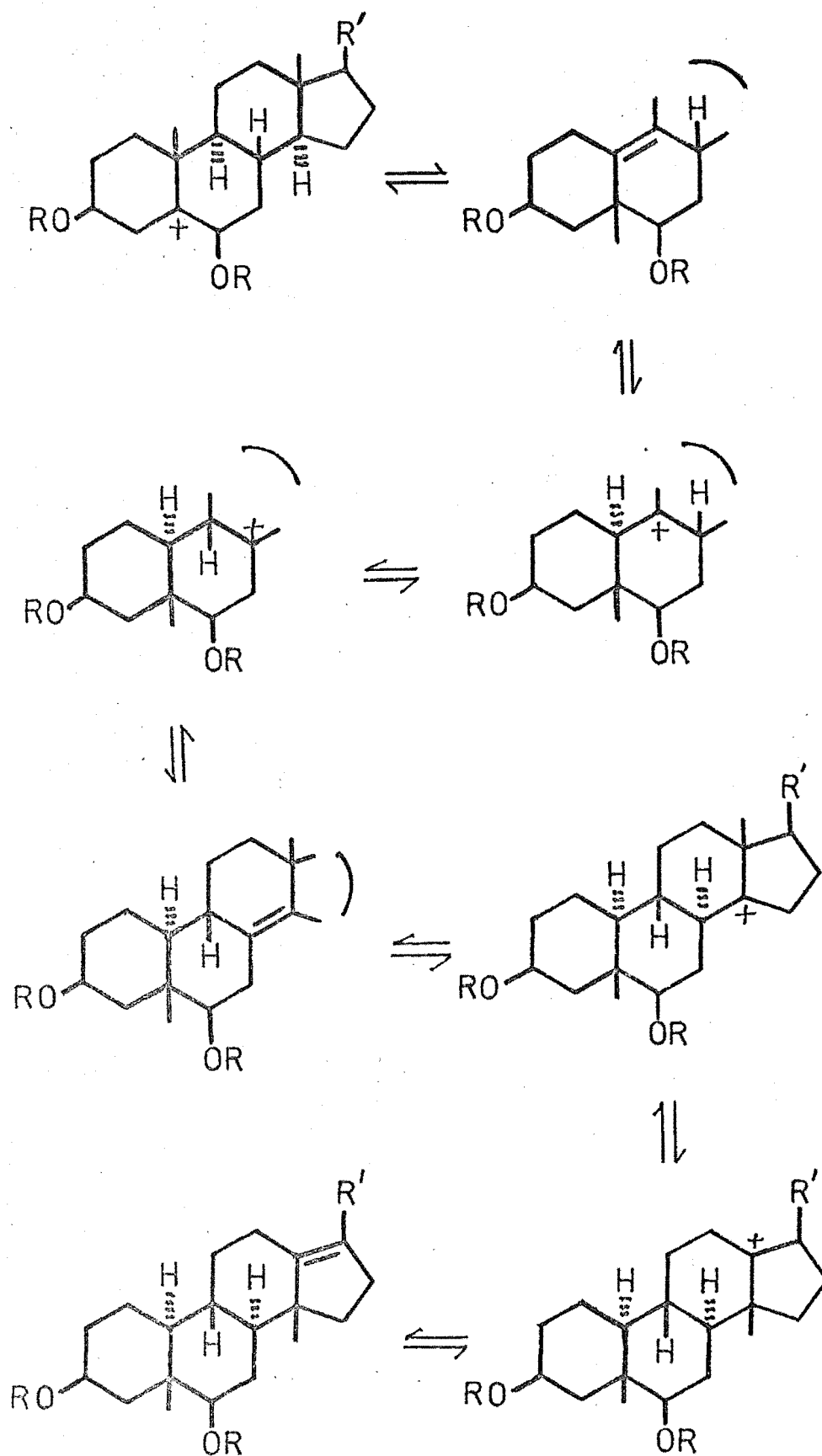
A concerted mechanism for the Westphalen rearrangement has, however, not been excluded by some authors. Jones and Marples<sup>23-27</sup> suggest that migration of the C(10)-methyl group may be, at least partially, concerted with the C(5)-O bond cleavage. Reaction of 3 $\beta$ -acetoxy-4,4-dimethyl-5-hydroxy-5 $\alpha$ -cholestan-6-one (8) with H<sub>2</sub>SO<sub>4</sub>-Ac<sub>2</sub>O-AcOH gave 3 $\beta$ -acetoxy-4,4,5 $\beta$ -trimethyl-19-norcholest-9(10)-en-6-one (9). These authors<sup>25</sup> argue that a discrete carbonium ion is unlikely to form at C(5) adjacent to a 6-ketone, and suggest migration of the C(10)-methyl is concerted with C(5)-O bond cleavage<sup>25</sup>. The assumption that a discrete carbonium ion will not form adjacent to a ketone is based on the reaction of 3 $\beta$ -acetoxy-5-hydroxy-5 $\alpha$ -cholestan-6-one (10a) with H<sub>2</sub>SO<sub>4</sub>-Ac<sub>2</sub>O-AcOH which gives 3 $\beta$ ,5-diacetoxy-5 $\alpha$ -cholestan-6-one (10b) and no rearranged products<sup>25</sup>. These authors do not consider the inductive effect of the C(4)-methyl groups in 3 $\beta$ -acetoxy-4,4-dimethyl-5-hydroxy-5 $\alpha$ -cholestan-6-one which will significantly lower the energy of a C(5)-carbonium ion. It is therefore not possible to exclude, a discrete carbonium ion as an intermediate in the reaction of 3 $\beta$ -acetoxy-4,4-dimethyl-5-hydroxy-5 $\alpha$ -cholestan-6-one (9) with H<sub>2</sub>SO<sub>4</sub>-Ac<sub>2</sub>O-AcOH.

The rearrangement of 6 $\beta$ -acetoxy-3 $\beta$ -methoxy-19-methyl-5 $\alpha$ -cholestan-5-ol (11a) with H<sub>2</sub>SO<sub>4</sub>-Ac<sub>2</sub>O-AcOH was shown to be 5.3 times faster than similar reaction of 6 $\beta$ -acetoxy-3 $\beta$ -methoxy-5 $\alpha$ -cholestan-5-ol (11b)<sup>26</sup>. This rate increase is offered by Jones and Marples as evidence for

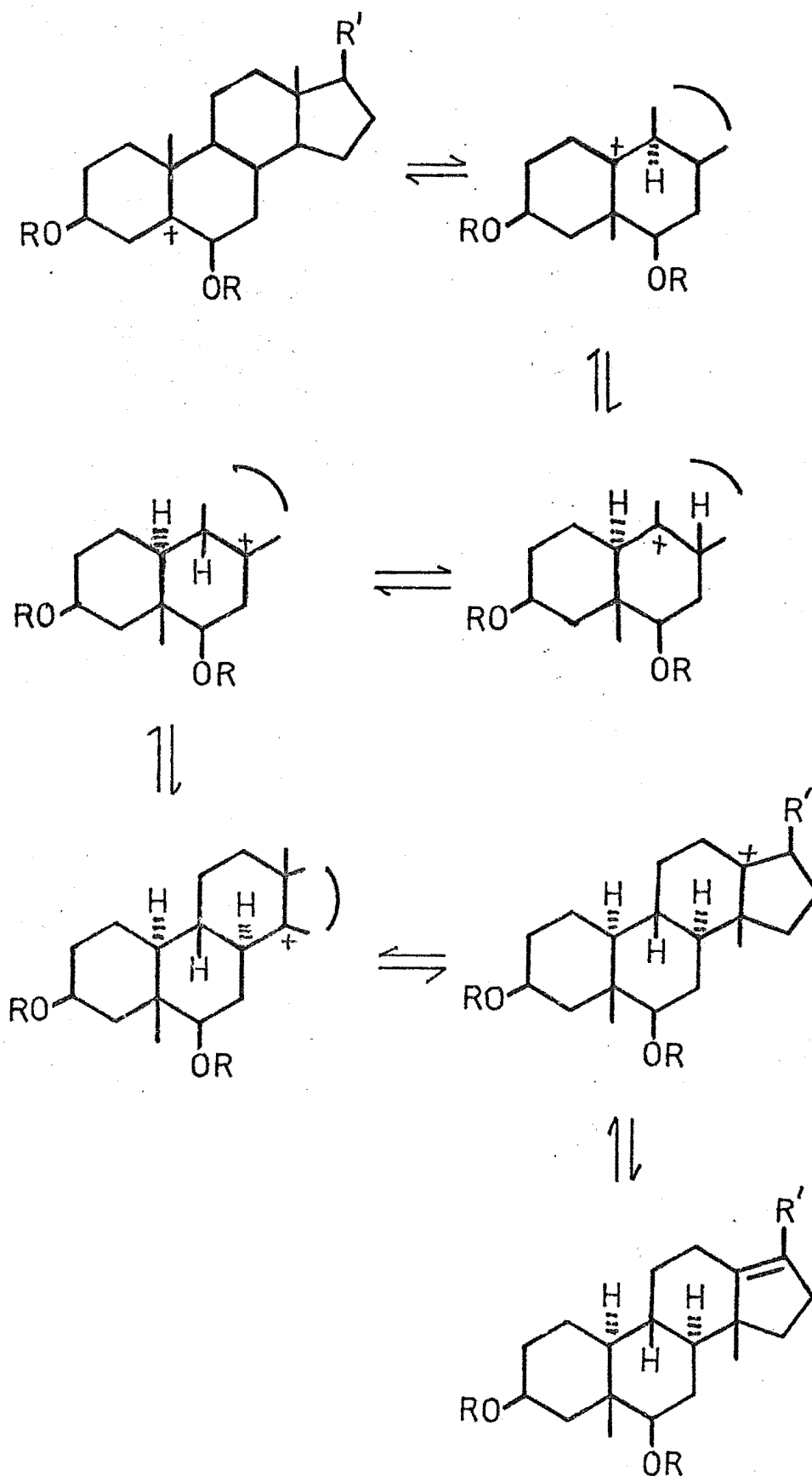


Scheme 2. Mechanism for the Backbone Rearrangement

Involving Olefin Intermediates



Scheme 3. Mechanism for the Backbone Rearrangement  
Involving Carbonium Ion Intermediates.



migration of the  $10\beta$ -alkyl group being concerted with C(5)-O cleavage. The C(19)-methyl group is compressed by the  $11\beta$ -hydrogen atom and suffers from two skew interactions with the C(1),C(10) and C(9), C(10) bonds (Figure 2)<sup>26</sup>. The authors argue that the

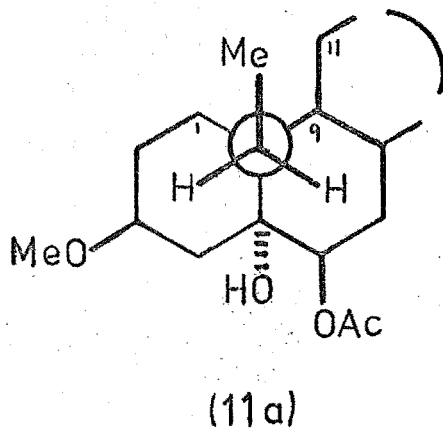


Figure 2

flattening of rings A and B with the formation of a discrete C(5)-carbonium ion does not relieve these interactions, but steric relief is possible in the transition state if alkyl group migration is concerted with C(5)-O bond cleavage<sup>26</sup>. The rate increase expected from the inductive effect of the  $10\beta$ -ethyl group in (11a) relative to the  $10\beta$ -methyl in (11b) was, however, not taken into account. This effect alone would lead to a three-fold rate increase in C(5)-O bond cleavage.

Jones and Marples<sup>27</sup> found that the rate of reaction of  $3\beta,6\beta$ -diacetoxy-5 $\alpha$ -cholestan-5-ol (5a),  $3\beta,6\beta$ -diacetoxy-4 $\alpha$ -methyl-5 $\alpha$ -cholestan-5-ol (13), and  $3\beta,6\beta$ -diacetoxy-4,4-dimethyl-5 $\alpha$ -cholestan-5-ol (14) in

$\text{H}_2\text{SO}_4\text{-Ac}_2\text{O-AcOH}$  were similar. The rate of reaction of  $3\beta,6\beta$ -diacetoxy  $4\beta$ -methyl- $5\alpha$ -cholestan-5-ol (15) under the same conditions was considerably faster. The authors argue that<sup>27</sup> the steric compression between the  $4\beta$ -methyl,  $10\beta$ -methyl, and  $6\beta$ -acetate would increase the rate, if the reaction is concerted. Conversely, compression between a  $4\alpha$ -methyl and the  $6\alpha$ -hydrogen would lead to a decrease in the rate of a concerted mechanism as this interaction is not relieved in the transition state. This rate data is however also consistent with the reaction proceeding via a discrete C(5)-carbonium ion. While a C(4)-methyl group would be expected to increase the rate of C(5)-O cleavage by ca 200<sup>28</sup> the formation of this ion will flatten rings A and B, causing the  $4\alpha$ -substituent and the  $6\alpha$ -hydrogen to move together. For substituents other than hydrogen this interaction would raise the energy of the C(5)-carbonium ion and the overall effect would lead to a decrease in the rate of C(5)-O bond cleavage.

Coxon, Hartshorn and Muir<sup>29,30</sup> suggest that the Westphalen rearrangement occurs in a stepwise manner involving the intermediacy of discrete carbonium ions.  $3\beta,6\beta$ -Diacetoxy- $5\alpha,9\beta$ -cholestan-5-ol (16) reacts with sulphuric acid-acetic acid-acetic anhydride to give two spirans (17) and (18) which result from migration of the C(1),C(10) bond to C(5) across the  $\alpha$ -face of the molecule (Figure 3)<sup>29</sup>. Both products have retained the configuration at C(5) of the starting alcohol and this is taken to exclude a synchronous mechanism. In the transition state C(5) will be nearly planar and much of the strain in the initial  $5\alpha,8\beta,9\beta,10\beta$ -skeleton will be relieved.<sup>29</sup> Dehydration with thionyl chloride of  $3\beta,6\beta$ -diacetoxy- $5\alpha,9\beta$ -cholestan-5-ol (16) gave spiran (18) formed with retention of configuration at C(5)<sup>30</sup>.

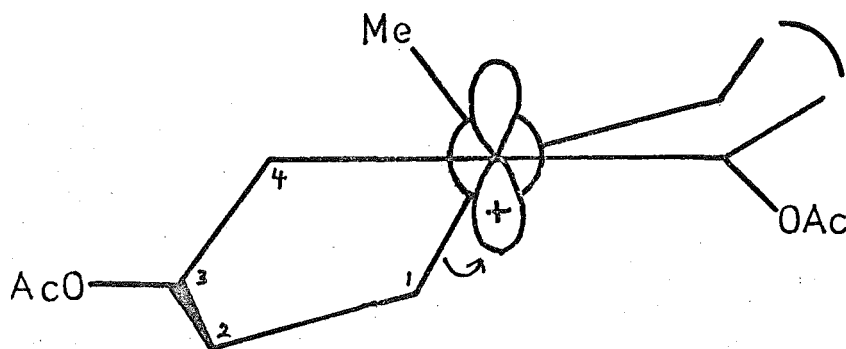


Figure 3

A minor but significant product in this reaction was  $3\beta,6\beta$ -diacetoxy-5-methyl- $5\beta,9\beta,10\beta,19$ -norcholest-7-ene (19). This latter compound arises from a rearrangement involving the trans,syn,cis system of the  $5\alpha,9\beta$ -cholestan-5-ol (16) to give a product with inversion of C(5) and retention at C(10) and C(9) and could therefore not be formed via a concerted pathway.<sup>30</sup>

In an attempt to identify the factors responsible for the backbone rearrangement Bascoul et al. studied the rearrangements of A-nor- and 19, A-bisnor- steroid epoxides.  $3\alpha,5\alpha$ -Epoxy- $3\beta$ -methyl-19, A-bisnorandrostan- $17\beta$ -ol (20) gave a backbone-rearranged product (21) on reaction with  $\text{BF}_3$ .etherate, but neither  $3\alpha,5\alpha$ -epoxy- $3\beta$ -methyl-A-norandrostan- $17\alpha$ -ol (22) or  $13\beta,17\beta$ -epoxy- $3\beta$ -hydroxy- $17\alpha$ -methyl-18,19-bisnorandrostan- $17\alpha$ -ol (23) gave products of backbone rearrangement under the same conditions. They suggest that three factors are responsible for backbone rearrangements.

(1) The molecule should be under intracyclic strain. This usually arises from the strain inherent in the normal steroid C/D ring.

junction. (ca 20 kJ/mole)<sup>90</sup> coupled with the steric interaction of the C(13)-methyl with the C(17)-side chain.

(2) Backbone rearrangement is facilitated when all the ring junctions are trans. For example, in a normal steroid system the substituents at the ring junction carbons are 5 $\alpha$ ,10 $\beta$ ,9 $\alpha$ ,10 $\beta$ ,14 $\alpha$ ,13 $\beta$ . In a backbone rearrangement, inversion of configuration normally occurs at each of these centres.

(3) If the driving force of the rearrangement is the relief of strain in the C/D ring junction the rearrangement will proceed until the carbonium ion is at C(13) or C(17).

Kirk and Shaw<sup>33</sup> found that intracyclic strain is not a prerequisite as D-homo-androst-5-ene (24) undergoes backbone rearrangement to give 5-methyl-19-norandrost-8(9)-enes. In this rearrangement epimerization occurs at all four ring junctions (C(5),C(10),C(13),C(14)) (Scheme 4)<sup>33</sup>. These authors now speak of backbone rearrangements as a search by the molecule for the most stable olefinic structures accessible by multiple Wagner-Meerwein hydride and methyl shifts.<sup>34</sup>

Several different reactions of steroids are believed to involve carbonium ion intermediates, but we will confine attention to the reactions of C(5)-alcohols with sulphuric acid-acetic acid-acetic anhydride<sup>92</sup> and C(5)-acetates with boron trifluoride etherate in acetic anhydride.

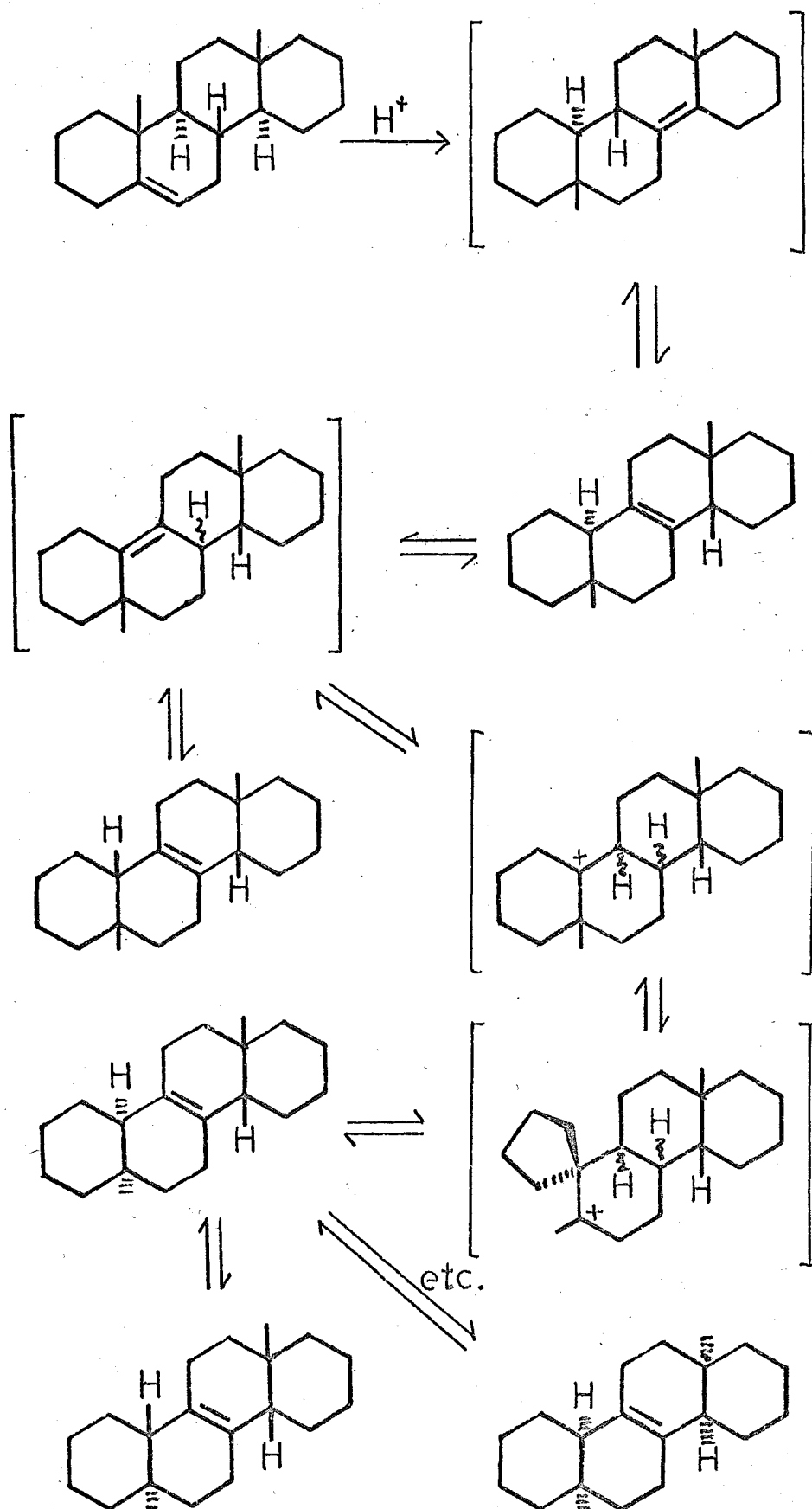
Reactions of 5-oxygenated steroids have been extensively studied, usually with substituents at positions in both rings A and B. Each substituent has an effect on the course of the reaction, for example, a 6 $\beta$ -acetate raises the energy of a C(5)-carbonium ion by its inductive effect and also makes hydride migration from C(8) to C(9) unfavourable.

Similarly, a  $3\beta$ -acetate will raise the energy of a C(5)- and a C(10)- carbonium ion.<sup>35</sup> The reaction of  $3\beta,6\beta$ -diacetoxy- $5\alpha$ -cholestan-5-ol (5a) with  $\text{H}_2\text{SO}_4\text{-Ac}_2\text{O-AcOH}$  will be controlled by a combination of the effects of both the  $3\beta$ - and  $6\beta$ - acetates and isolating the individual effects of each acetate is difficult.

Comparatively few studies have been made on steroids with only one substituent on either ring A or ring B. Reaction of  $6\beta$ -acetoxy- $5\alpha$ -cholestan-5-ol (25) with  $\text{H}_2\text{SO}_4\text{-Ac}_2\text{O-AcOH}$ <sup>17</sup> gave 50% of products arising from a C(10)-carbonium ion and three products, comprising 25% of the reaction mixture which were not identified.  $4\beta$ -Acetoxy- $5\alpha$ -cholestan-5-ol (26b) with  $\text{H}_2\text{SO}_4\text{-Ac}_2\text{O-AcOH}$  gave backbone rearranged products<sup>36</sup>, while  $3\beta$ -acetoxy- $5\alpha$ -cholestan-5-ol (27a) gave only  $3\beta$ -acetoxycholest-4-ene and  $3\beta$ -acetoxycholest-5-ene<sup>17,37,38,39</sup>.

The present work has been concerned with the investigation of factors influencing backbone rearrangements. For this purpose the synthesis and reactions of steroids with oxygenated substituents at C(4) and C(5) were carried out. Attempts to synthesize and react analogous steroids in the unnatural series ( $9\alpha,10\alpha$ , and  $9\beta,10\beta$ ) were unsuccessful.

Scheme 4.    Rearrangement of D-Homoandrost-5-ene.





## DISCUSSION

### (1) Acid Catalysed Reactions of 4-Acetoxy-5-hydroxy- and 4,5-Diacetoxy- Cholestanes

It has been known for some time that the "Westphalen" rearrangements of  $5\alpha$ -hydroxy steroids are sensitive to substituents in rings A and B. Substituents can affect the rate and products of reaction. The importance of substituents in determining the course of reaction is evident from a comparison of the reactions of  $3\beta,6\beta$ -diacetoxy- $5\alpha$ -cholestan-5-ol (5a) and the  $6\alpha$ -epimer (28) with sulphuric acid-acetic acid-acetic anhydride; while the  $6\beta$ -acetoxy compound (5a) largely gives the rearranged  $5\beta$ -methyl- $\Delta^9$ -compound (6a),<sup>12</sup> the  $6\alpha$ -acetoxy compound (28) yields only unrearranged  $\Delta^4$ -products<sup>82,91</sup>. It is apparent that changing the orientation of the C(6) substituent from  $\beta$  to  $\alpha$  excluded migration of the C(10)-methyl to C(5). This can be understood by considering the way in which rings A and B adjust to the change in hybridization which occurs at C(5) as the C(5)-O bond cleaves. For the C(10)-methyl to migrate the vacant p-orbital of the C(5)-carbonium ion must be eclipsed with the C(10)-methyl  $\sigma$ -bond. For such an alignment of orbitals, both rings A and B must flatten (conformation I). The 1,3 diaxial interaction between the C(10)-methyl and the  $6\beta$ -acetate present in the starting material is relieved on the formation of the carbonium ion in conformation (I). The carbonium ion may adopt two other conformations (Scheme 5). One of these (II) has ring A as a boat and ring B as a chair. The other conformation (III) has ring A as a chair and ring B as a boat. It

is thought that the carbonium ion will initially form in conformation (I) as this minimizes interactions of the C(5) leaving group with the  $1\alpha$ -,  $3\alpha$ -,  $7\alpha$ -, and  $9\alpha$ -hydrogens (Figure 4). Methyl migration from C(10) to C(5) can occur more rapidly than conformational changes of (I) to (II) and (III) (Scheme 5).

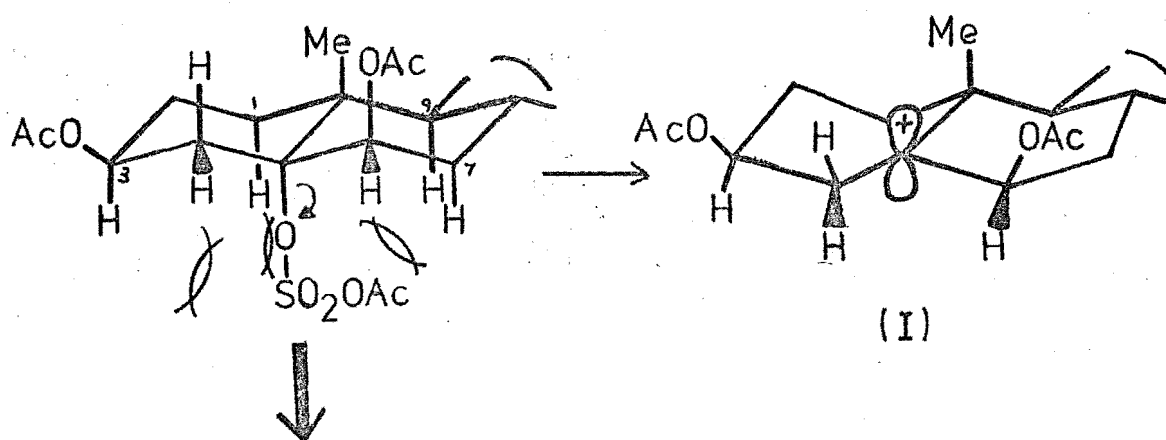
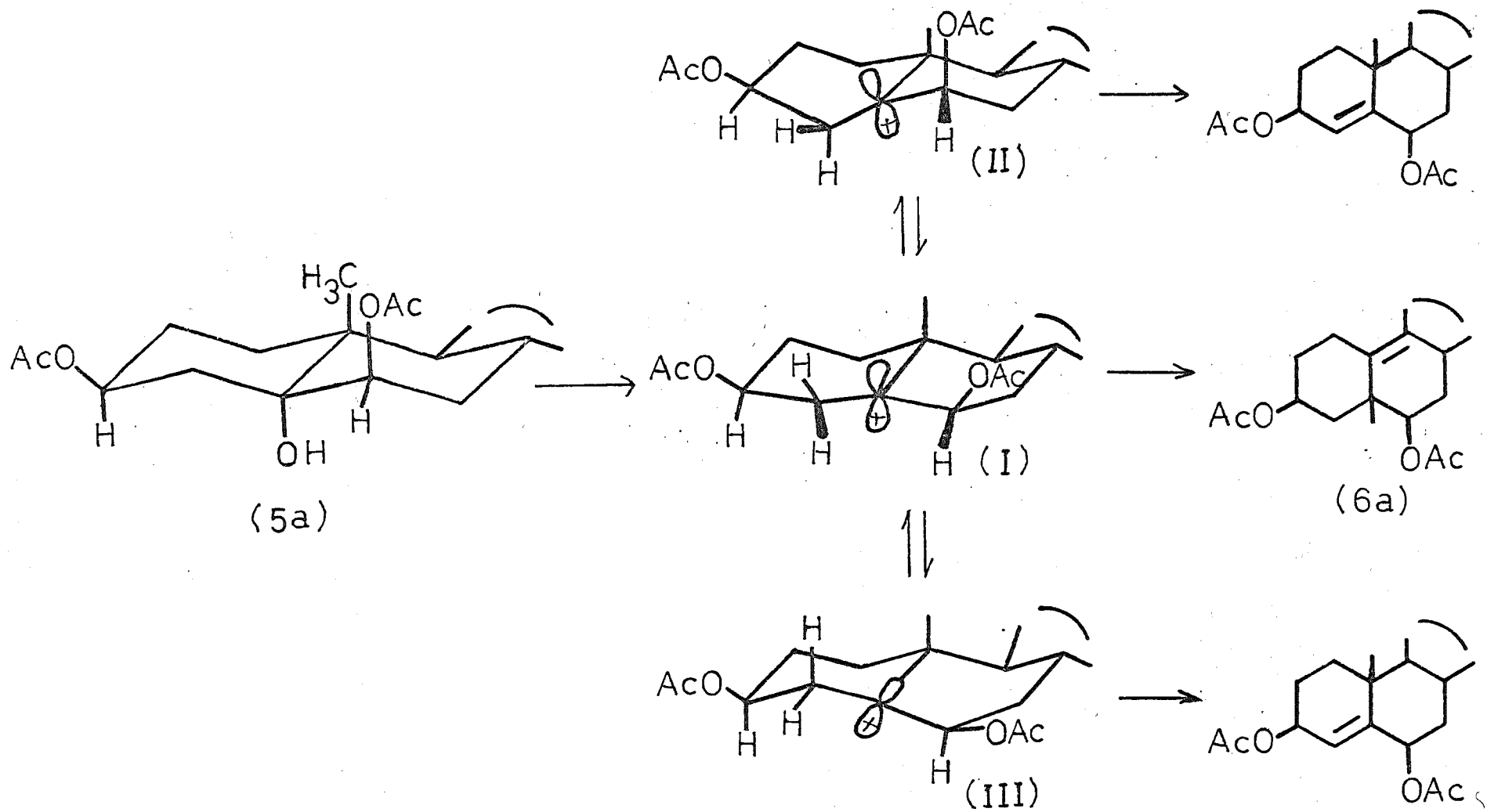


Figure 4



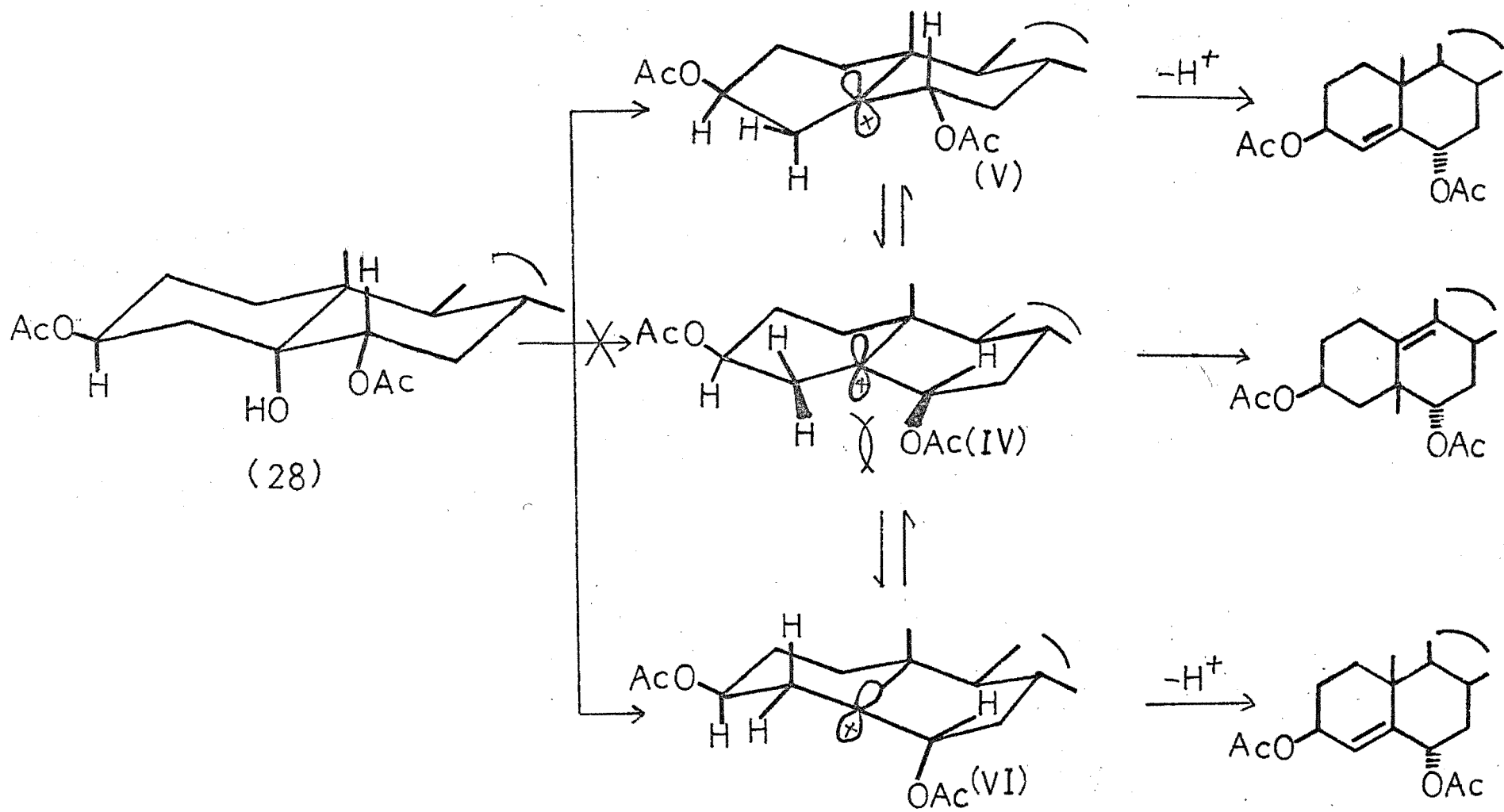
Scheme 5.

Conformational Changes of the C(5)-Carbonium Ion.

The ring A half-boat, ring B half-boat conformation (IV) for the carbonium ion formed from  $3\beta,6\alpha$ -diacetoxy- $5\alpha$ -cholestan-5-ol (28) can be shown from Dreiding models to involve an unfavourable interaction between  $4\alpha$ -hydrogen and the  $6\alpha$ -acetate. This interaction will favour conformations (V) and (VI). In conformations (V) and (VI) the interaction between the C(4) and C(6) substituents is relieved. Elimination of the  $4\alpha$ -hydrogen can occur from conformation (V) to give  $3\beta,6\alpha$ -diacetoxycholest-4-ene. From conformation (VI) the  $4\beta$ -hydrogen can be abstracted by base, to give  $3\beta,6\alpha$ -diacetoxycholest-4-ene (Scheme 6).

Methyl migration has also been found to occur in the reaction of  $4\beta$ -acetoxy- $5\alpha$ -cholestan-5-ol (26b) with  $\text{H}_2\text{SO}_4\text{-Ac}_2\text{O-AcOH}$ .<sup>36</sup> As well as the "Westphalen" product,  $4\beta$ -acetoxy- $5\beta$ -methyl-19-norcholest-9(10)-ene (29) (60%), two extensively rearranged compounds,  $4\beta$ -acetoxy- $5\beta$ -methyl-19-norcholest-8(14)-ene (30) and  $4\beta$ -acetoxy- $5\beta,14\beta$ -dimethyl-18,19-bisnorcholest-13(17)-ene (31) are formed. The high yield of products resulting from C(10)-methyl migration can be understood by considering the conformation of the initially produced C(5)-carbonium ion. With the formation of the C(5)-carbonium ion both rings A and B flatten and in this conformation (VII) the 1,3-diaxial interaction between the  $4\beta$ -acetate and the  $10\beta$ -methyl is relieved. The vacant p-orbital of the carbonium ion is eclipsed with the C(10)-methyl  $\sigma$ -bond allowing methyl migration to occur. Two other conformations of the C(5)-carbonium ion (VIII) and (IX) are shown in Scheme 7. Formation of the C(5)-ion in these conformations (VIII and IX) involves movement of both C(4) and C(6) and is expected to be slower than methyl migration. The flat conformation (VII) of the carbonium

Scheme 6. Conformational Changes in the Reaction of  
3 $\beta$ ,6 $\alpha$ -Diacetoxy-5 $\alpha$ -cholestan-5-ol with Acid.

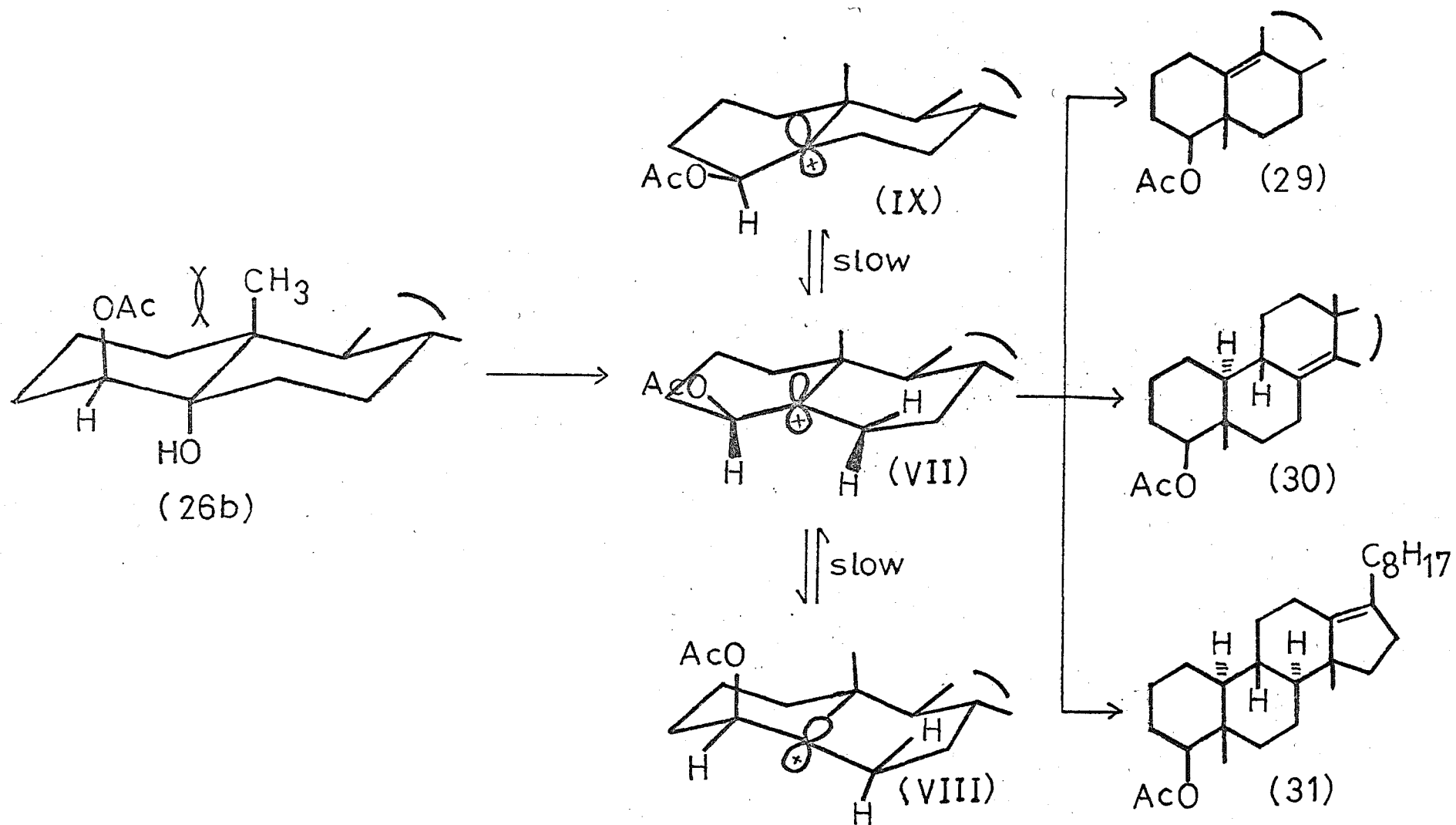


ion will be formed initially as interactions of the C(5) leaving group with the 1 $\alpha$ -, 3 $\alpha$ -, 7 $\alpha$ - and 9 $\alpha$ - hydrogens is minimized in the formation of the ion in this conformation (of Figure 3). Changes in the conformation of the carbonium ion from VII to (VIII) and (IX) can occur in competition with C(10)-methyl migration.

To test the validity of these mechanistic ideas, we undertook to examine a system in which an interaction between a 4 $\alpha$ - and a 6 $\alpha$ -substituent would make unfavourable the flat carbonium ion conformation (XIII) and thereby exclude the formation of methyl migration products. An investigation of the stereochemistry of hydrogen loss from the intermediate carbonium ion was also undertaken. The systems chosen for study were 4 $\alpha$ -acetoxy-5 $\alpha$ -cholestan-5-ol (32b) and 4 $\alpha$ ,5-diacetoxy-5 $\alpha$ -cholestane (32c). The information obtained from this study can be readily compared with that of the corresponding 4 $\beta$ ,5 $\alpha$ -isomers.<sup>36</sup>

The required steroids were synthesized from cholest-4-ene by reaction with osmium tetroxide followed by reduction of the osmate ester with bisulphite. This resulted in a mixture of 4 $\alpha$ ,5-dihydroxy-5 $\alpha$ -cholestane (32a) and 4 $\beta$ ,5-dihydroxy-5 $\beta$ -cholestane (33a) which was separated by chromatography. Acetylation with acetic anhydride-pyridine gave the corresponding 4-acetoxycholestan-5-ols (32b) and (33b).

Treatment of 4 $\alpha$ -acetoxy-5 $\alpha$ -cholestan-5-ol (32b) under the usual Westphalen dehydration conditions<sup>13,18</sup> led to extensive decomposition of the steroid. Even with only trace amounts of sulphuric acid the reaction was extremely rapid. The reaction was quenched after 3 seconds and the product mixture shown to contain 4 $\alpha$ -acetoxy-5 $\alpha$ -cholestan-5-ol (32b) (80%) and 4 $\alpha$ -acetoxycholest-5-ene (34a) (20%).



Scheme 7: Reaction of 4β-Acetoxy-5α-cholestan-5-ol.

This olefin was identical to that prepared by dehydration of 4 $\alpha$ -acetoxy-5 $\alpha$ -cholestan-5-ol (32b) with thionyl chloride. The n.m.r. spectrum showed the C(4)-proton as a doublet ( $J = 5\text{Hz}$ ) centred at  $\delta$  5.43, the axial 4 $\beta$ -proton as a broad ( $\frac{W_h}{2} 10\text{Hz}$ ) peak at  $\delta$  5.32, and the acetate as a singlet at  $\delta$  2.08. With a longer reaction time of 10 seconds a 3:1 mixture of 4 $\alpha$ -acetoxycholest-5-ene (34b) and 4 $\beta$ -acetoxycholest-5-ene (35) was obtained. The identity of 4 $\beta$ -acetoxycholest-5-ene (35) was verified by comparison with an authentic sample prepared by dehydration of 4 $\beta$ -acetoxy-5 $\alpha$ -cholestan-5-ol (26b) with thionyl chloride. The n.m.r. spectrum showed the C(4)-proton as a doublet ( $J = 3\text{Hz}$ ) centred at  $\delta$  5.72, the equatorial 4 $\alpha$ -proton as a multiplet ( $\frac{W_h}{2} = 5\text{Hz}$ ) at  $\delta$  5.30, and the acetate as a singlet at  $\delta$  2.00. The differences in the chemical shifts of the acetate groups in the n.m.r. spectra of the 4 $\alpha$ - and 4 $\beta$ -acetoxycholest-4-enes facilitated the analysis of the product mixture. In separate experiments, 4 $\alpha$ -acetoxycholest-5-ene (34b) and 4 $\beta$ -acetoxycholest-5-ene (35) were treated with  $\text{H}_2\text{SO}_4\text{-Ac}_2\text{O-AcOH}$  and each gave a similar mixture of 4 $\alpha$ -acetoxycholest-5-ene and 4 $\beta$ -acetoxycholest-5-ene. Equilibration studies of the 4-acetoxycholest-5-enes using the milder hydrofluoroboric acid failed because the 4 $\beta$ -epimer readily eliminates acetic acid to give cholest-3,5-diene (38) thereby complicating any kinetic study.

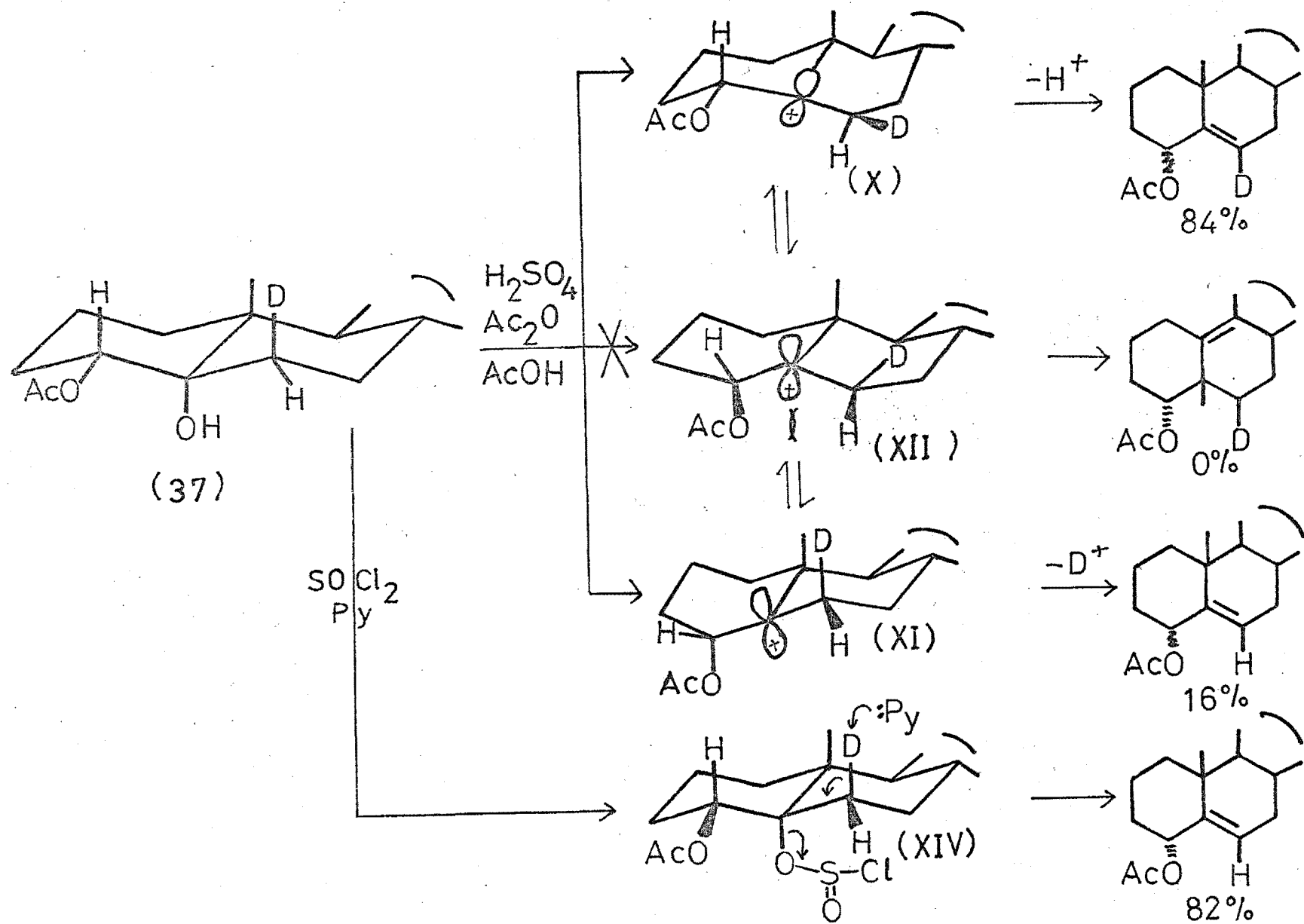
To determine which hydrogen is lost in the formation of the 4-acetoxycholest-5-enes from 4 $\alpha$ -acetoxy-5 $\alpha$ -cholestan-5-ol (32b) a deuterium atom was introduced to the 6 $\beta$ -position by reacting 5 $\alpha$ ,6 $\alpha$ -epoxycholestan-4 $\alpha$ -ol (36) with lithium aluminium deuteride. Acetylation of the 5 $\alpha$ -cholestan-4 $\alpha$ ,5-diol-6 $\beta$ -d gave 4 $\alpha$ -acetoxy-5 $\alpha$ -cholestan-5-ol-6 $\beta$ -d (37) shown by mass spectrometry to be >96%



deuterated. After reaction of 4 $\alpha$ -acetoxy-5 $\alpha$ -cholestan-5-ol-6 $\beta$ -d (37) with  $\text{H}_2\text{SO}_4\text{-Ac}_2\text{O-AcOH}$ , the mixture of 4 $\alpha$ - and 4 $\beta$ -acetoxycholest-5-enes was analysed by mass spectrometry. The product mixture had retained  $89 \pm 5\%$  of the original deuterium label. Treatment of the product mixture with  $\text{LiAlH}_4$  in ether gave a mixture of 4 $\alpha$ - and 4 $\beta$ -hydroxycholest-5-enes which was shown by mass spectrometry to contain  $84 \pm 4\%$  deuterium label.

Dehydration of 4 $\alpha$ -acetoxy-5 $\alpha$ -cholestan-5-ol-6 $\beta$ -d (37) with thionyl chloride followed by treatment of the product with  $\text{LiAlH}_4$  in ether, gave cholest-5-en-4 $\alpha$ -ol (34a) in high yield. Mass spectrometry showed the presence of  $18.5 \pm 1.5\%$  deuterium label.

These results can be rationalized in terms of conformational changes of the initially produced carbonium ion as in Scheme 8. The carbonium ion conformation (XII), in which both rings A and B flatten and the C(5) vacant p-orbital is eclipsed with the C(10)-methyl  $\sigma$ -bond, possesses an unfavourable interaction between the 4 $\alpha$ -acetate and the 6 $\alpha$ -hydrogen. This conformation would be unfavourable and no products arising from it, (e.g. methyl migration products) are observed. The carbonium ion is able to adopt conformations (X) or (XI) (Scheme 5). The former conformation (X) with the 4 $\alpha$ -acetate equatorial is probably less energetic than conformation (XI) where the acetate is axial. The majority of the product (84%) does in fact arise from conformation (X) as this leads to products which retain the 6 $\beta$ -deuterium label. The loss of ca 16% of the deuterium label indicates that the alternative conformation (XI) in which the 4 $\alpha$ -acetate is axial is formed to some extent. The unfavourable axial orientation of the acetate may be offset by the formation of a cyclic intramolecular acetonium ion.



Scheme 8. Conformational Changes in the Reactions of 4 $\alpha$ -Acetoxy-5 $\alpha$ -cholestan-5-ol.

The loss of 82% of the axial  $6\beta$ -deuterium found for the reaction of 4 $\alpha$ -acetoxy-5 $\alpha$ -cholestan-5-ol-6 $\beta$ -d (37) with thionyl chloride is consistent with an expected E2 elimination mechanism, as the  $6\beta$ -deuterium and the 5 $\alpha$ -leaving group are anti-periplanar.

An alternative method of heterolysis of the C(5)-O bond involves reaction of a 5 $\alpha$ -acetate with boron trifluoride etherate in acetic anhydride. Such reactions give higher yields of extensively rearranged products compared with corresponding reactions of 5 $\alpha$ -alcohols with  $\text{H}_2\text{SO}_4\text{-Ac}_2\text{O-AcOH}$ .<sup>13,36</sup>

Reaction of 4 $\alpha$ ,5 $\alpha$ -diacetoxycholestane (32c) with  $\text{BF}_3\cdot\text{etherate-Ac}_2\text{O}$  was rapid and a time of 25 seconds was selected in order to minimize further reaction of the products. The reaction gave a more complex mixture than the reaction of 4 $\alpha$ -acetoxy-5 $\alpha$ -cholestan-5-ol with  $\text{H}_2\text{SO}_4\text{-Ac}_2\text{O-AcOH}$ . The compounds isolated were: an inseparable mixture<sup>40</sup> of cholest-3,5-diene (38) and cholest-4,6-diene (39) (53%) with an  $[\alpha]_D$  of  $-84^\circ$  (compared with  $-123^\circ$  for cholest-3,5-diene<sup>41</sup> (38) and  $+4^\circ$  for cholest-4,6-diene<sup>42</sup>); 4 $\alpha$ -acetoxycholest-5-ene (34b) (5%); 4 $\beta$ -acetoxy cholest-5-ene (35) (5%); 5 $\alpha$ -cholestan-4-one (4%); and unreacted 4 $\alpha$ ,5-diacetoxy-5 $\alpha$ -cholestane (32c) (9%) (Scheme 9).

Changing the orientation of the C(5)-substituent can have a marked effect on the course of the reaction. Backbone-rearranged products have been obtained from reactions of 4 $\beta$ ,5-epoxy-5 $\beta$ -cholestane and 5,6 $\beta$ -epoxy-5 $\beta$ -cholestane with boron trifluoride etherate<sup>43</sup>. The vacant p-orbital of the C(5)-carbonium ion generated in this reaction is apparently able to eclipse with the C(10)-methyl  $\sigma$ -bond (Scheme 10). On the other hand, reaction of 3 $\beta$ ,6 $\beta$ -diacetox-5 $\beta$ -cholestan-5-ol (41) with  $\text{H}_2\text{SO}_4\text{-Ac}_2\text{O-AcOH}$ <sup>44</sup> gave only products of elimination involving

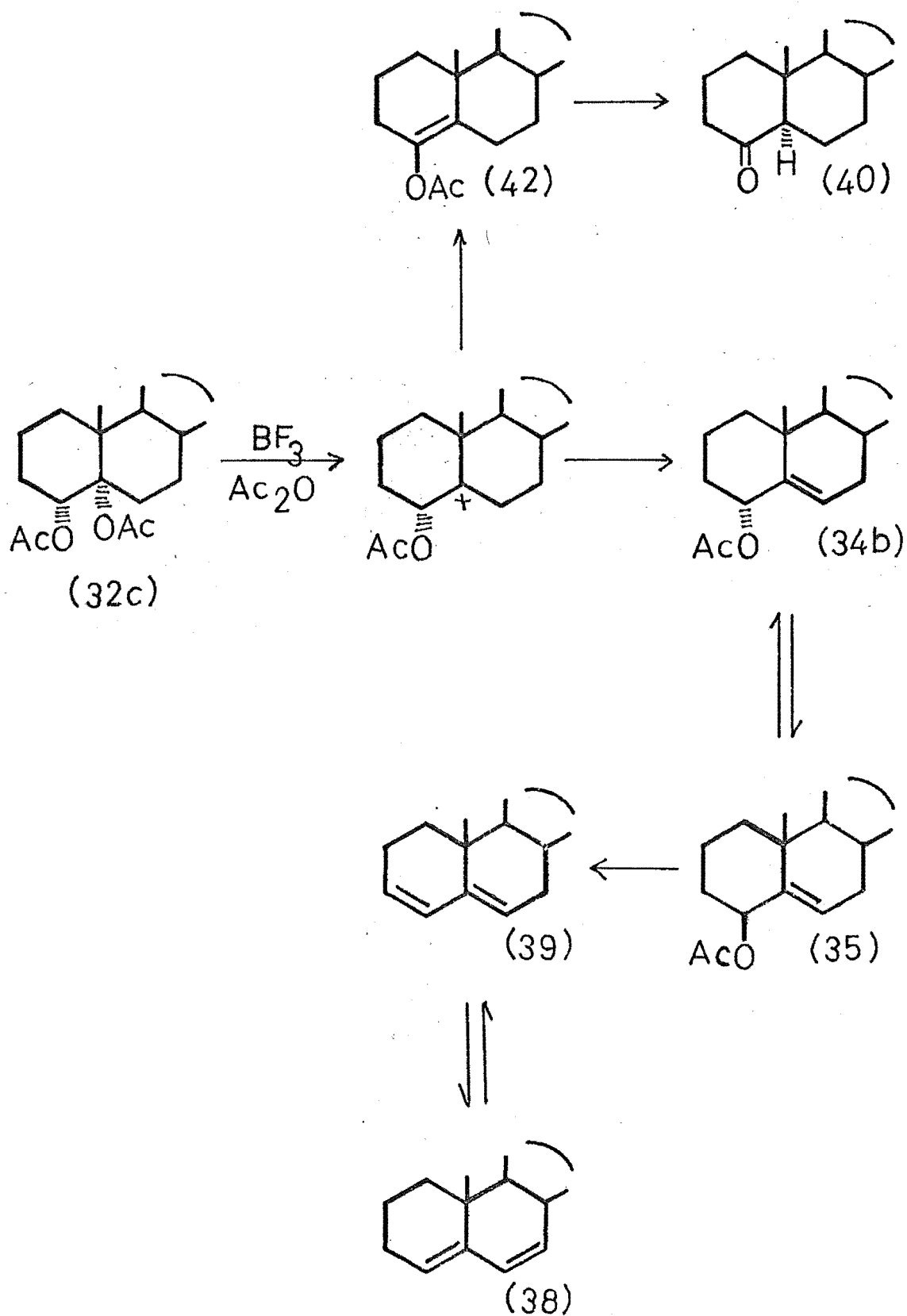
loss of the 4- or 6 $\alpha$ - hydrogens demonstrating that the conformational changes needed to allow methyl migration do not occur (Scheme 11).

The reaction of 4 $\beta$ -acetoxy-5 $\beta$ -cholestan-5-ol (33b) with  $\text{H}_2\text{SO}_4\text{-Ac}_2\text{O-AcOH}$  has been studied. 4 $\beta$ -Acetoxy-5 $\beta$ -cholestan-5-ol (33b) was reacted with a catalytic amount of sulphuric acid in  $\text{Ac}_2\text{O-AcOH}$ . The reaction was slower than the similar reaction of the 4 $\alpha$ ,5 $\alpha$ -analogue. After 30 minutes of reaction, no unreacted 4 $\beta$ -acetoxy-5 $\beta$ -cholestan-5-ol (33b) could be detected and the product mixture consisted of; 4 $\alpha$ -acetoxycholest-5-ene (34b) (5%), 4 $\beta$ -acetoxycholest-5-ene (35) (4%), 5 $\alpha$ -cholestan-4-one (40) (17%), 4 $\beta$ ,5 $\beta$ -diacetoxycholestane (33c) (69%), and several unidentified polar products (8%). The n.m.r. and i.r. spectra were consistent for each structure. The formation of 5 $\alpha$ -cholestan-4-one (40) is not unprecedented as an analogous product was obtained by Rowland<sup>44</sup> in a similar reaction of 3 $\beta$ ,6 $\beta$ -diacetoxy-5 $\beta$ -cholestan-5-ol (41). 5 $\alpha$ -cholestan-4-one probably arises from elimination of the 4 $\alpha$ -hydrogen from the C(5)-carbonium ion in conformation (XV) to give 4-acetoxycholest-4-ene (42) which undergoes hydrolysis on work-up (Scheme 12).

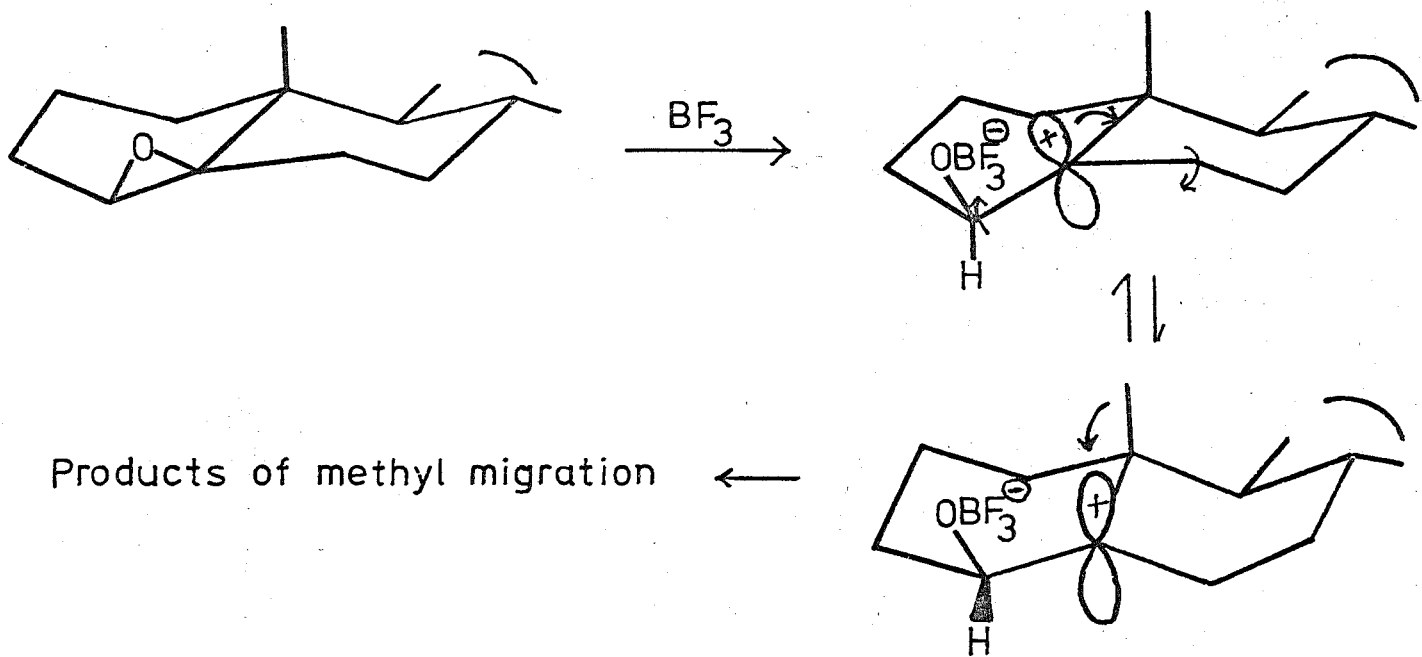
Reaction of 4 $\beta$ ,5 $\beta$ -diacetoxycholestane (33c) with boron trifluoride etherate in acetic anhydride gave a product mixture which was similar to that obtained from the reaction of 4 $\beta$ -acetoxy-5 $\beta$ -cholestan-5-ol (33b) with  $\text{H}_2\text{SO}_4\text{-Ac}_2\text{O-AcOH}$ , and consisted of; 4 $\alpha$ -acetoxycholest-5-ene (34b) (3%), 4 $\beta$ -acetoxycholest-5-ene (35) (9%), 5 $\alpha$ -cholestan-4-one (40) (35%), unreacted 4 $\beta$ , 5 $\beta$ -diacetoxycholestane (33c) (19%), and two unidentified polar products (10%).

All the products arising from the reaction of the 4 $\beta$ -acetoxy-5 $\beta$ -hydroxy- and 4 $\beta$ ,5 $\beta$ -diacetoxy-5 $\beta$ - cholestanes can be accounted for if

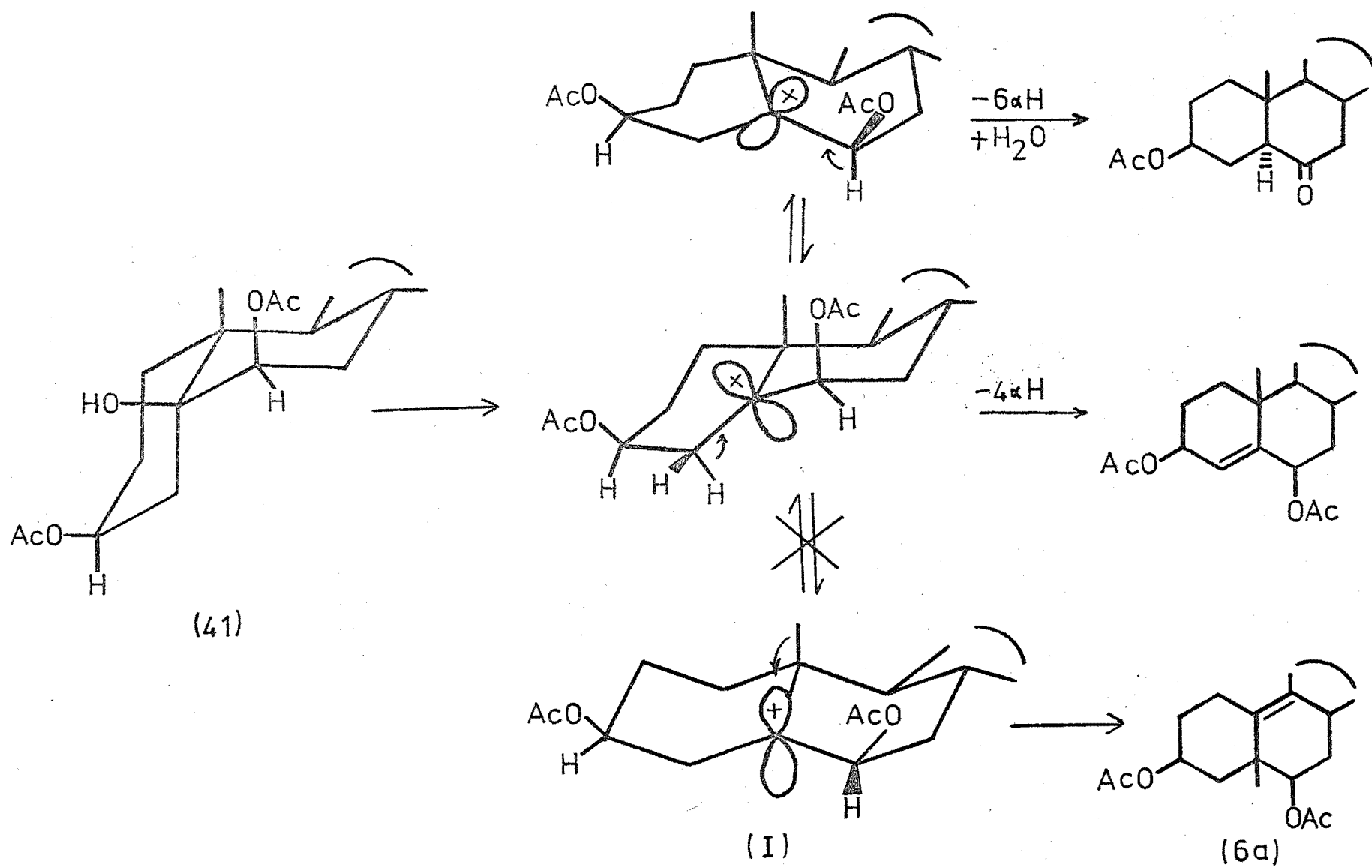
Scheme 9. Reaction of 4 $\alpha$ ,5-Diacetoxy-5 $\alpha$ -cholestane  
with  $\text{BF}_3 \cdot \text{Et}_2\text{O} - \text{Ac}_2\text{O}$



Scheme 10. Conformation Changes in the Reaction of 4 $\beta$ ,5 $\beta$ -Epoxycyclohexane with  $\text{BF}_3$ .

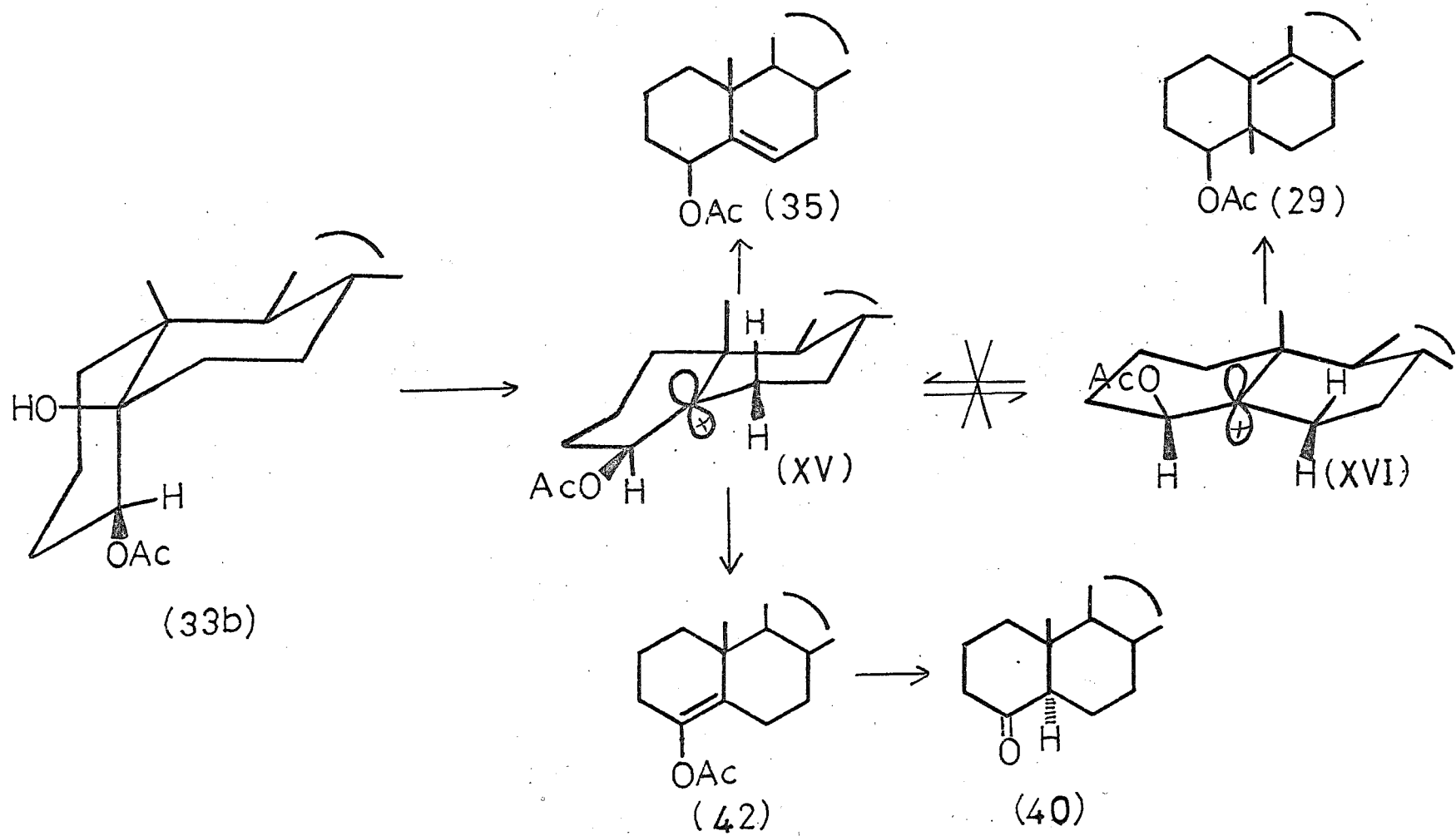


Scheme 11. Conformational Changes on Reaction of  
 3 $\beta$ ,6 $\beta$ -Diacetoxy-5 $\beta$ -cholestan-5-ol with H<sub>2</sub>SO<sub>4</sub>-Ac<sub>2</sub>O-AcOH



we assume the reaction proceeds through conformation (XV) of the C(5) carbonium ion. Loss of the  $4\alpha$ -hydrogen or the  $6\beta$ -hydrogen is possible from this conformation. To attain a conformation of the carbonium ion (XVI) in which the vacant p-orbital at C(5) is eclipsed with the C(10)-methyl  $\sigma$ -bond considerable movement of the carbon atoms in both rings A and B must occur (Scheme 12). It is thought that the chair-chair conformation (XV) is thermodynamically more stable than the half-boat, half-boat conformation (XVI).





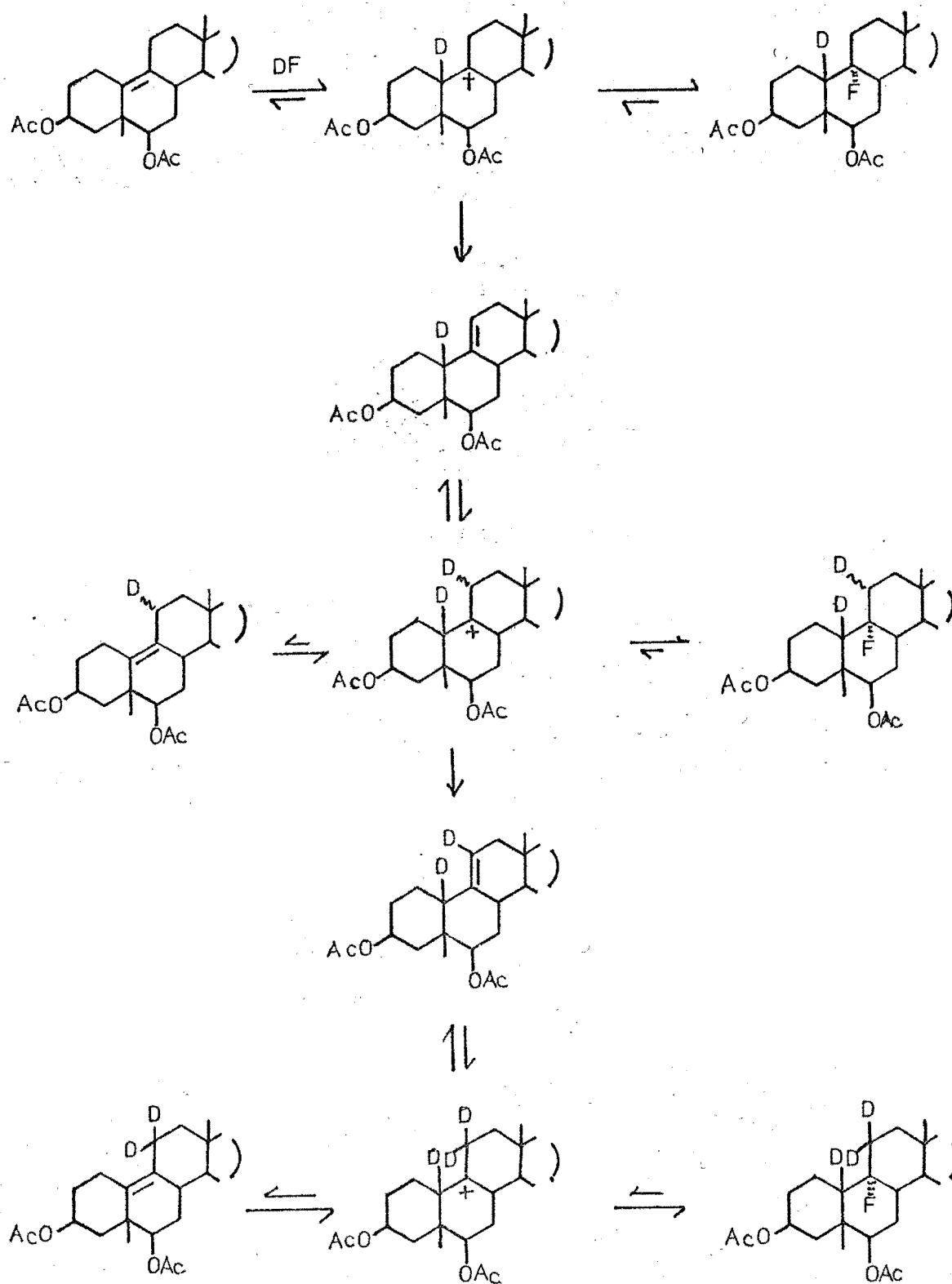
Scheme 12: Reaction of 4 $\beta$ -Acetoxystero-5-ol with  $H_2SO_4$ -Ac $_2$ O-AcOH.

## (2) Rearrangements in Deuterated Solvents

Studies of backbone rearrangements with deuterated acids have revealed several apparent anomalies in reaction mechanisms. Cholesterol and the Westphalen diacetate (6a) on reaction with  $\text{DF}$ ,<sup>45,46</sup> and holamine (43) and methylholaphylline (44) on reaction with  $\text{D}_2\text{SO}_4$ <sup>47,48</sup> result in backbone rearrangement with multiple deuterium incorporation. Euphenol acetate (48)<sup>49</sup> and friedel-3-ene (1)<sup>6</sup> similarly undergo backbone rearrangement in  $\text{TsOH-CD}_3\text{COOD}$  and  $\text{ZnCl}_2\text{-DOAc}$  respectively with multiple deuterium incorporation but with a significant proportion of the reaction (10% and 25% respectively) proceeding by a non-stop mechanism. Friedel-3-ene (1) and glutin-5(10-ene (4) undergo backbone rearrangement with  $\text{CF}_3\text{COOD-CHCl}_3$  but with the incorporation of only one deuterium atom.<sup>7</sup> Rearrangement of des-A-androst-11-en-8 $\beta$ ,17 $\beta$ -diol (46) with  $\text{DF}$ <sup>83</sup> followed by treatment with methanol-KOH gave a backbone rearranged product with deuterium incorporation only at C(11). The effect of the ring D hydroxy group is unknown, but may lower the energy of activation for the non-stop mechanism. The mechanism of backbone rearrangement thus seems to be sensitive to the reaction conditions.

Multiple deuterium incorporation can be accounted for by a series of olefin-carbonium ion equilibria (Scheme 13)<sup>45</sup>. Deuterium incorporation in the 5 $\beta$ -methyl group has been observed in the isomerisation of methylholaphylline (44) to isomethylholaphylline (47) with  $\text{D}_2\text{SO}_4$ . Incorporation of deuterium is thought to arise via the intermediacy of a cyclopropane,<sup>49</sup> but the situation is not simple since deuterium incorporation has not been observed in the 14 $\alpha$ -methyl group<sup>47,48</sup>. In contrast, deuterium is thought to be present in both

Scheme 13. Reaction of the Westphalen Diacetate with DF  
Showing Incorporation of Deuterium.

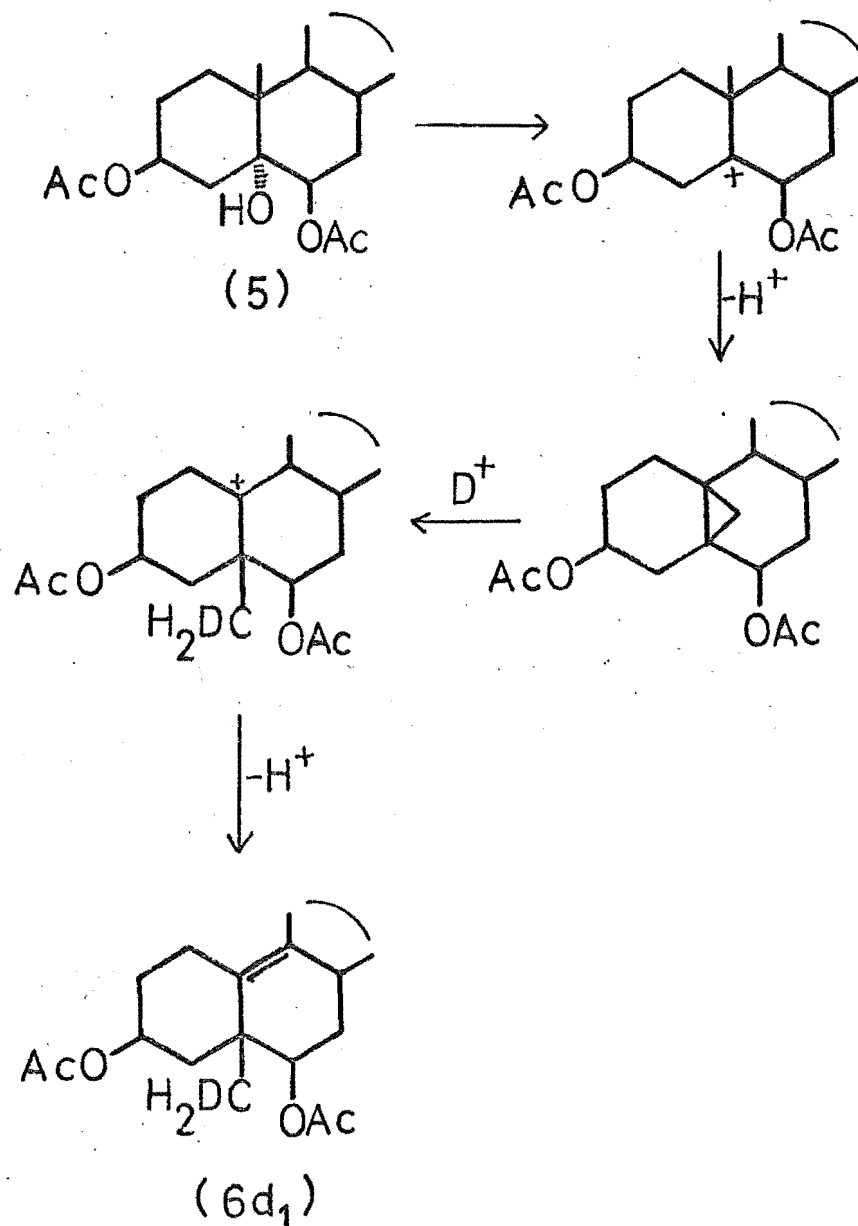


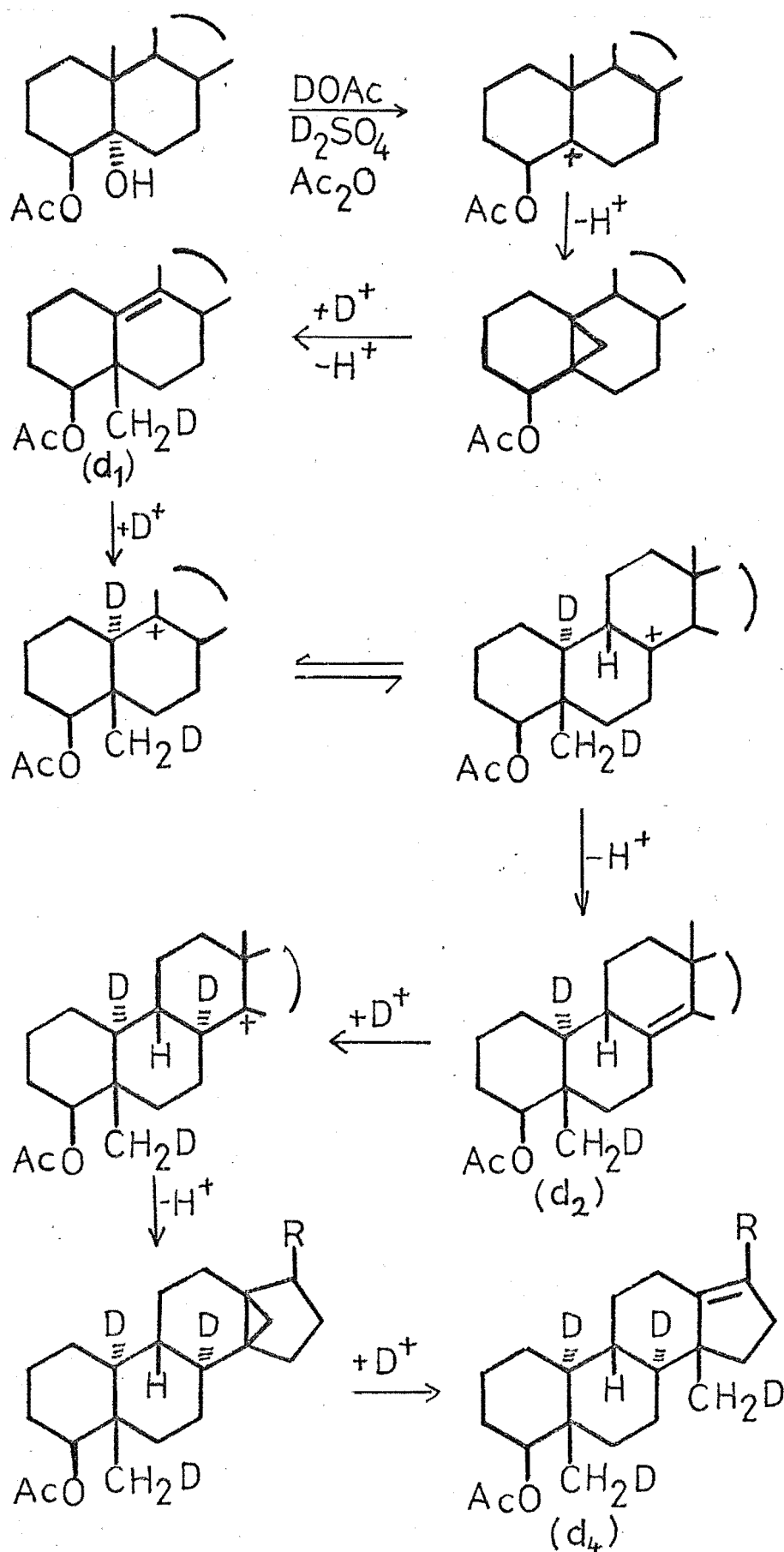
the 8 $\beta$ - and 14 $\alpha$ - methyl groups in isoeuphenol (48) obtained from rearranging euphenol (45) in deuterated solvents.<sup>49</sup>

In the present study we have investigated the reactions of 3 $\beta$ ,6 $\beta$ -diacetoxy-5 $\alpha$ -cholestan-5-ol (5a) and 4 $\beta$ -acetoxy-5 $\alpha$ -cholestan-5-ol (26b) in H<sub>2</sub>SO<sub>4</sub>-Ac<sub>2</sub>O-DOAc. The reaction conditions chosen are relatively mild and the substrates were chosen to give specific information. If the 10 $\beta$ -methyl group of 3 $\beta$ ,6 $\beta$ -diacetoxy-5 $\alpha$ -cholestan-5-ol (5a) formed a cyclopropane intermediate in the Westphalen rearrangement to 3 $\beta$ ,6 $\beta$ -diacetoxy-5 $\beta$ -methyl-19-norcholest-9(10)-ene (6a), deuterium incorporation would be observed in the 5 $\beta$ -methyl group of the product when deuterated acids are used (Scheme 14). Deuterium incorporation would also be observed if the  $\Delta^{9(10)}$ -olefinic bond isomerises as in Scheme 13<sup>45</sup>. 4 $\beta$ -Acetoxy-5 $\alpha$ -cholestan-5-ol (26b) reacts with H<sub>2</sub>SO<sub>4</sub>-Ac<sub>2</sub>O-AcOH to give products of both partial and complete backbone rearrangement.<sup>36</sup> If the rearrangement of 4 $\beta$ -acetoxy-5 $\alpha$ -cholestan-5-ol (26b) was carried out in D<sub>2</sub>SO<sub>4</sub>-DOAc-Ac<sub>2</sub>O, deuterium incorporation in any of the rearranged products would indicate either the intermediacy of a cyclopropane in methyl migration or a carbonium ion-olefin-carbonium ion mechanism (Scheme 15).

Rearrangement of 3 $\beta$ ,6 $\beta$ -diacetoxy-5 $\alpha$ -cholestan-5-ol (5a) in acetic anhydride and acetic acid-d<sub>4</sub> (>98% d<sub>4</sub>) with a catalytic amount of sulphuric acid gave 3 $\beta$ ,6 $\beta$ -diacetoxy-5 $\beta$ -methyl-19-norcholest-9(10)-ene (6a) identical in all respects to an authentic sample prepared using undeuterated acids<sup>50</sup>. The 70ev mass spectrum gave several intense peaks, m/e 426 (100%; M<sup>+</sup> - HOAc), 411 (7%; M<sup>+</sup> - HOAc-CH<sub>3</sub>), 384 (7%) 366 (36%; M<sup>+</sup> - 2HOAc), 351 (64%; M<sup>+</sup> - 2HOAc-CH<sub>3</sub>), 325 (27%). Intensity measurements (M<sup>+</sup> - HOAc) and M<sup>+</sup> - HOAc + 1) (426 and 427)

Scheme 14. A Possible Mechanism for the Incorporation of Deuterium into the 5 $\beta$ -Methyl Group of the Westphalen Diacetate Formed in Deuterated Acids.





Scheme 15. Possible Mechanism for the Incorporation of  
Deuterium in the Rearrangement of 4 $\beta$ -Acetoxy-  
5 $\alpha$ -cholestan-5-ol in Deuterated Acids.

peaks and on the ( $M^+ - 2\text{HOAc}$ ) and ( $M^+ - 2\text{HOAc} + 1$ ) (366 and 367) peaks showed no difference between the rearranged samples obtained from reaction in the deuterated and undeuterated systems. N.m.r. integral measurements were also identical for the two rearranged samples.

Rearrangement of  $4\beta$ -acetoxy- $5\alpha$ -cholestan-5-ol (26b) under the conditions employed in the literature<sup>36</sup> was repeated to obtain reference samples of the rearranged products. Reaction of this steroid with  $\text{H}_2\text{SO}_4\text{-Ac}_2\text{O-AcOH}$  gave a mixture of  $4\beta$ -acetoxy- $5\beta$ -methyl-19-norcholest-9(10)-ene (29),  $4\beta$ -acetoxy- $5\beta$ -methyl-19-norcholest-8(14)-ene (30),  $4\beta$ -acetoxy- $5\beta$ ,14 $\beta$ -dimethyl-18,19-bisnorcholest-13(17)-ene (31), and  $5\alpha$ -cholestan-4-one (40)<sup>51</sup>. Small samples of each of these compounds were obtained by column and preparative thin layer chromatography. The  $\Delta^{13(17)}$ -olefin (31) could not be obtained pure and was contaminated with traces of  $5\alpha$ -cholestan-4-one (40).

Repeating the reaction but using deuterated acetic acid ( $>95\% \text{d}_1$ ; prepared from sodium dried acetic anhydride and  $\text{D}_2\text{O}$ ) and a catalytic amount of sulphuric acid with dry acetic anhydride gave a mixture of the same olefins. Small samples of each of the  $\Delta^{9(10)}$ -,  $\Delta^{8(14)}$ -, and  $\Delta^{13(17)}$ -olefins (29), (30), and (31) were obtained by column and preparative thin layer chromatography. The  $\Delta^{13(17)}$ -olefin (31) could not be obtained free of  $5\alpha$ -cholestan-4-one (40). Mass spectral intensity measurements were made on the  $M^+$  and ( $M^+ + 1$ ) (428 and 429) and on the ( $M^+ - \text{HOAc}$ ) and ( $M^+ - \text{HOAc} + 1$ ) (368 and 369) peaks for each rearranged compound. Measurements for these peaks were reproducible (Table 1). The olefins

Table 1. Intensity Measurements of  $M^+/(M^+ + 1)$  and  $(M^+ - HOAc)/(M^+ - HOAc + 1)$  Peaks for Olefins (29), (30) and (31) and ketone (40) obtained from Rearrangements of 4 $\beta$ -Acetoxy-5 $\alpha$ -cholestan-5-ol

Olefin	$M^+/(M^+ + 1)$ (428/429)*			$(M^+ - HOAc)/(M^+ - HOAc + 1)$ (368/369)**		
	Calc	From H <sup>+</sup>	From D <sup>+</sup>	Calc.	From H <sup>+</sup>	From D <sup>+</sup>
$\Delta^{9(10)}$ (29)	0.32	0.29	0.32	0.30	0.30	0.34
$\Delta^{8(14)}$ (30)	0.32	0.31	0.34	0.30	0.38	0.31
$\Delta^{13(17)}$ (31)	0.32	0.32	0.30	0.30	0.35	0.28
4-ketone (40)						
(386/387)**	0.30	0.36	0.40			

\* Measured ratios  $\pm$  0.02

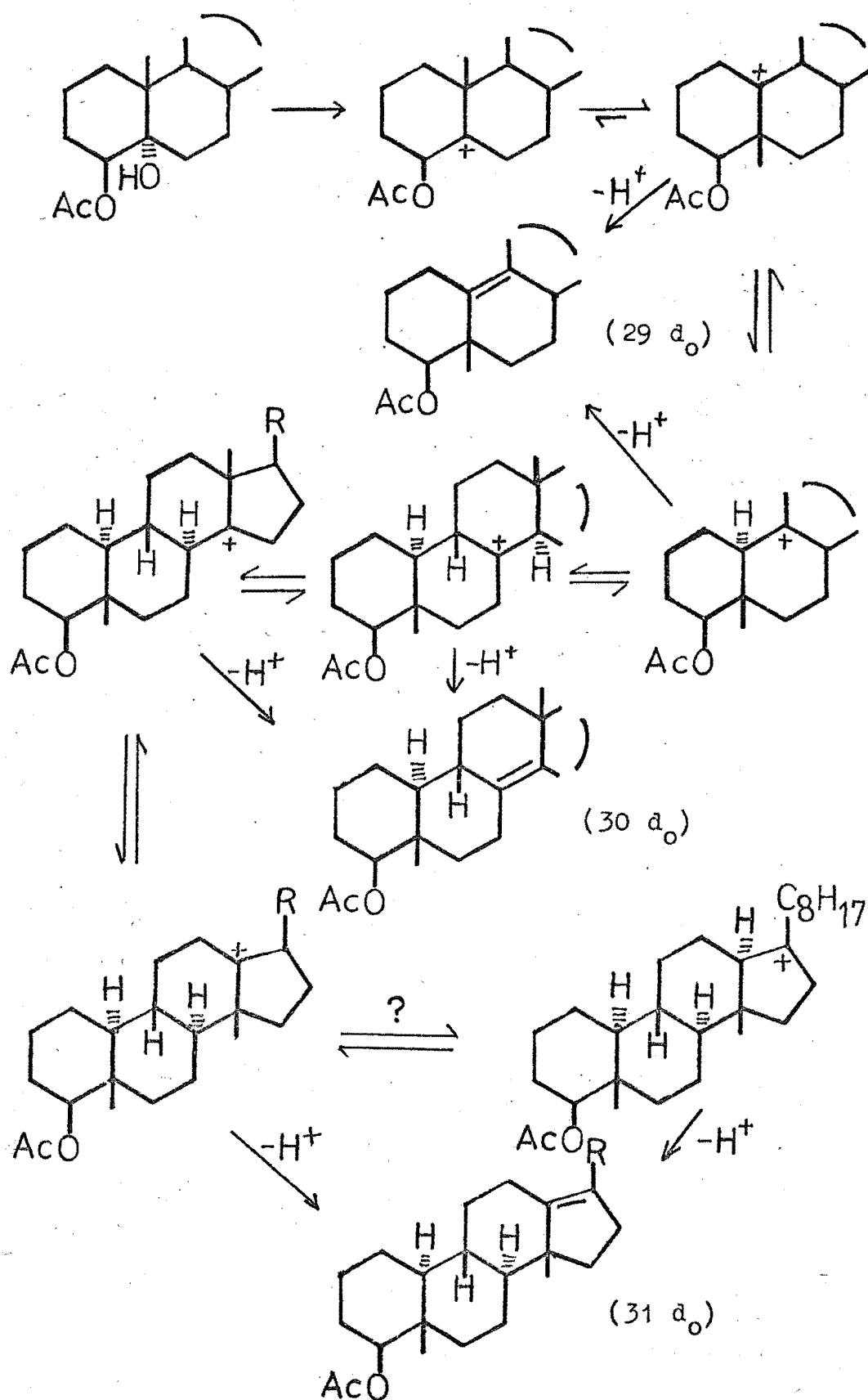
\*\* Measured ratios  $\pm$  0.04



obtained from rearrangement of 4 $\beta$ -acetoxy-5 $\alpha$ -cholestan-5-ol (26b) in deuterated and undeuterated acid gave identical mass spectra showing that there was no deuterium incorporation when the reaction was carried out in deuterated acid.

The absence of deuterium in the rearranged products obtained from 3 $\beta$ ,6 $\beta$ -diacetoxy-5 $\alpha$ -cholestan-5-ol (5a) and 4 $\beta$ -acetoxy-5 $\alpha$ -cholestan-5-ol (26b) on reaction with H<sub>2</sub>SO<sub>4</sub>-DOAc-Ac<sub>2</sub>O excludes the intermediacy of cyclopropanes in the migration of the angular methyl groups<sup>52</sup>. In a similar manner it is possible to exclude the intermediacy of olefins in the rearrangement. Olefin isomerisations such as those found by Jacquesy *et al.*<sup>45</sup> (Scheme 13) can be ruled out. As a concerted mechanism for the backbone rearrangement is not feasible, it can be concluded that the rearrangement involves a series of rapidly equilibrating carbonium ion intermediates. Base abstraction of a proton from these carbonium ion intermediates accounts for the formation of the partially rearranged<sup>23</sup> 3 $\beta$ ,6 $\beta$ -diacetoxy-5 $\beta$ -methyl-19-norcholest-9(10)-ene (6a), 4 $\beta$ -acetoxy-5 $\beta$ -methyl-19-norcholest-9(10)-ene (29), and 4 $\beta$ -acetoxy-5 $\beta$ -methyl-19-norcholest-8(14)-ene (30) (Scheme 16).

Scheme 16. Rearrangement of 4 $\beta$ -Acetoxy-5 $\alpha$ -cholestan-5-ol  
in Deuterated Acid.



(3) Reactions of 5 $\alpha$ -Monosubstituted Steroids

Acid catalysed reactions of 5 $\alpha$ -oxygenated steroids, in which stereochemical constraints on rings A and B due to substituents are either limited or absent, have been previously studied in some detail. The conformation of the C(5)-carbonium ion with both rings A and B flattened should arise more easily in these systems than in a constrained system. Methyl migration from C(10) to C(5) can occur if the vacant p-orbital at C(5) is eclipsed with the C(10)-methyl  $\sigma$ -bond. The most extensively studied systems of this type are the 3 $\beta$ -substituted- 5 $\alpha$ - hydroxy- and acetoxy- cholestanes. The equatorial 3 $\beta$ -substituent offers little steric interference to conformational changes in rings A and B.

Several workers <sup>17,37,39,53</sup> have examined the reaction of 3 $\beta$ -acetoxy-5 $\alpha$ -cholestan-5-ol (27a) with  $H_2SO_4$ - $Ac_2O$ - $AcOH$ . 3 $\beta$ -Acetoxycholest-4-ene (49) and 3 $\beta$ -acetoxycholest-5-ene (50) are the only products that have been isolated. Reaction of 3 $\beta$ -fluoro-5 $\alpha$ -cholestan-5-ol (51) with  $H_2SO_4$ - $AcOH$ - $Ac_2O$  gave 3 $\beta$ -fluorocholest-5-ene (52) in high yield <sup>54</sup>. 3 $\beta$ ,5 $\alpha$ -Diacetoxy cholestane (27b) with  $BF_3$ .etherate- $Ac_2O$  gave 3 $\beta$ -acetoxycholest-5-ene (50) (66%) along with 3 $\beta$ -acetoxy-5 $\beta$ ,14 $\beta$ -dimethyl-18,19-bisnorcholest-13(17)-ene (53) (25%) <sup>57</sup>. Reaction of 3 $\beta$ -acetoxy-5 $\alpha$ -fluorocholestane (54) with  $BF_3$ .etherate in benzene gave 3 $\beta$ -acetoxycholest-5-ene (50) (80%) and 3 $\beta$ -acetoxy-5 $\beta$ ,14 $\beta$ -dimethyl-18,19-bisnorcholest-13(17)-ene (53) (20%) <sup>55,81</sup>. 3 $\alpha$ -Acetoxy-5-fluoro-5 $\alpha$ -cholestane (55), on reaction with  $BF_3$ .etherate in benzene, gave a similar product mixture to that obtained from the 3 $\beta$ -epimer <sup>55</sup>. Deamination of 3 $\beta$ -acetoxy-5-amino-5 $\alpha$ -cholestane (56) with nitrous acid,

known<sup>38,56</sup> to produce a "hot" carbonium ion at C(5), gave, in high yield, 3 $\beta$ -acetoxycholest-4-ene (49) and 3 $\beta$ -acetoxycholest-5-ene (50)<sup>38</sup>. The lack of rearrangement from the 5 $\alpha$ -amino steroid is thought to result from the facility with which the basic nitrite species abstracts a hydrogen from either C(4) or C(6).

The course of reaction in the above examples seems to be particularly sensitive to solvent, acid, and leaving group. Reactions of 5 $\alpha$ -acetates and 5 $\alpha$ -fluorides with BF<sub>3</sub>.etherate in solvents such as acetic anhydride or benzene, in which no general base is present,<sup>57,58,89</sup> give high yields of extensively rearranged products. The other reaction conditions described have basic species present and proton abstraction from C(4) or C(6) occurs in preference to rearrangement.

There are no known reactions of 5 $\alpha$ -monosubstituted steroids with Lewis acids and so undertook to study the reactions of some 5 $\alpha$ -substituted steroids. The following reactions were examined;

- (1) 5 $\alpha$ -Cholestan-5-ol (57a) with H<sub>2</sub>SO<sub>4</sub>-Ac<sub>2</sub>O-AcOH.
- (2) 5-Acetoxy-5 $\alpha$ -cholestane (57b) with BF<sub>3</sub>.etherate-Ac<sub>2</sub>O.
- (3) 5-Chloro-5 $\alpha$ -cholestane (58) with silver oxide-methanol in benzene or nitrobenzene.

5 $\alpha$ -Cholestan-5-ol (57a) was prepared by the reaction of LiAlH<sub>4</sub> on 5 $\alpha$ ,6 $\alpha$ -epoxycholestane and was reacted with H<sub>2</sub>SO<sub>4</sub>-AcOH-Ac<sub>2</sub>O<sup>59</sup>. The product mixture was a crystalline material and t.l.c. showed no trace of unreacted 5 $\alpha$ -cholestan-5-ol (57a). The presence in the n.m.r. spectrum of a multiplet at  $\delta$  5.27 ppm ( $\frac{W}{2}$  8Hz) was consistent with the product being a mixture of cholest-4-ene (59) and cholest-5-ene (60). This olefinic signal in the n.m.r. spectrum results from overlap of the

C(4)-proton multiplet ( $\delta$  5.28 ppm;  $W_{\frac{h}{2}}$  7Hz) of cholest-4-ene (59) and the C(6)-proton doublet ( $\delta$  5.25 ppm  $J = 4\text{Hz}$ ) of cholest-5-ene (60). A prepared (1:1) mixture of cholest-4-ene (59) and cholest-5-ene (60) showed a multiplet at  $\delta$  5.27 similar in shape to that obtained for the reaction mixture. The specific rotation of the reaction product mixture was  $+29^\circ$ . This compares to  $+66^\circ$  for cholest-4-ene (59) and  $-56^\circ$  for cholest-5-ene (60) <sup>60</sup> and indicates that the mixture is a 7:3 ratio of cholest-4-ene and cholest-5-ene. It was not possible to separate the two olefins by g.l.c. on 2% SE30, and a preliminary study using high pressure liquid chromatography was not successful. This latter technique showed the presence of a trace of a third olefin, possibly  $5\beta,14\beta$ -dimethyl-18,19-bisnorcholest-13(17)-ene (61). Facilities were not available to extend these studies, but it was apparent that high-pressure liquid chromatography would have been a valuable aid to this work.

5-Acetoxy-5 $\alpha$ -cholestane (57b) was prepared by acetylation of 5 $\alpha$ -cholestan-5-ol (57a) with acetyl chloride in chloroform and dimethylaniline. Some elimination to cholest-4-ene (59) and cholest-5-ene (60) occurred under these reaction conditions and the yield of acetate was low. Rearrangement of 5-acetoxy-5 $\alpha$ -cholestane (57b) was effected using  $\text{BF}_3$ .etherate in dry acetic anhydride. The oily product mixture was shown by tlc and n.m.r. not to contain any unreacted 5-acetoxy-5 $\alpha$ -cholestane. The presence of a multiplet ( $W_{\frac{h}{2}}$  8Hz) at  $\delta$  5.25 ppm in the n.m.r. spectrum indicated the presence of both cholest-4-ene (59) and cholest-5-ene (60). The presence of  $5\beta,14$ -dimethyl-18,19-bisnorcholest-13(17)-ene (61) was inferred from the n.m.r. spectrum. The  $\text{C}(26)\text{H}_3$  and  $\text{C}(27)\text{H}_3$  signals occurred as a

doublet ( $J = 6\text{Hz}$ ) centred at  $\delta 0.83$  ppm and the  $\text{C}(21)\text{H}_3$  as a doublet ( $J = 7\text{Hz}$ ) centred at  $\delta 0.95$  ppm. The  $5\beta$ -methyl and the  $14\beta$ -methyl occurred as singlets at  $\delta 0.82$  and  $\delta 0.88$  ppm respectively. Double irradiation of the  $\text{C}(20)$ -allylic proton at 88 Hz down-field from the  $\text{C}(21)\text{H}_3$  doublet did not lead to any visible collapse of the  $\text{C}(21)\text{H}_3$  doublet but this would be obscured by the methyl peaks of cholest-4-ene which are coincident with the  $\text{C}(21)\text{H}_3$  doublet. Separation of  $5\beta, 14\beta$ -dimethyl-18,19-bisnorcholest-13(17)-ene (61) from cholest-4-ene and cholest-5-ene was possible by glc using 2% SE30 and by high-pressure liquid chromatography. In this manner it was shown that  $5\beta, 14\beta$ -dimethyl-18,19-bisnorcholest-13(17)-ene (61) made up ca 33% of the product mixture and cholest-4-ene and cholest-5-ene together made up ca 67%.

Cholest-5-ene (60) was reacted with  $\text{BF}_3$ .etherate in acetic anhydride under conditions similar to the reaction of 5-acetoxy-5 $\alpha$ -cholestane with  $\text{BF}_3$ .etherate. No isomerisation or rearrangement occurred. Rearrangement of cholest-5-ene (60) did however occur on reaction with  $\text{BF}_3$ .etherate acetic anhydride in the presence of a small amount of acetic acid (0.3%). After 2 hours at  $100^\circ$  a mixture containing  $5\beta, 14\beta$ -dimethyl-18,19-bisnorcholest-13(17)-ene (61) (ca 70%) and two unidentified olefins was obtained <sup>84</sup>. This arrangement may be due to the presence of  $\text{HF}$  generated from the reaction of  $\text{BF}_3$  with the available protons. This backbone rearrangement of cholest-5-ene may be similar to the known rearrangement of cholest-5-ene with toluene-p-sulphonic acid in acetic acid and cyclohexane <sup>92</sup>.

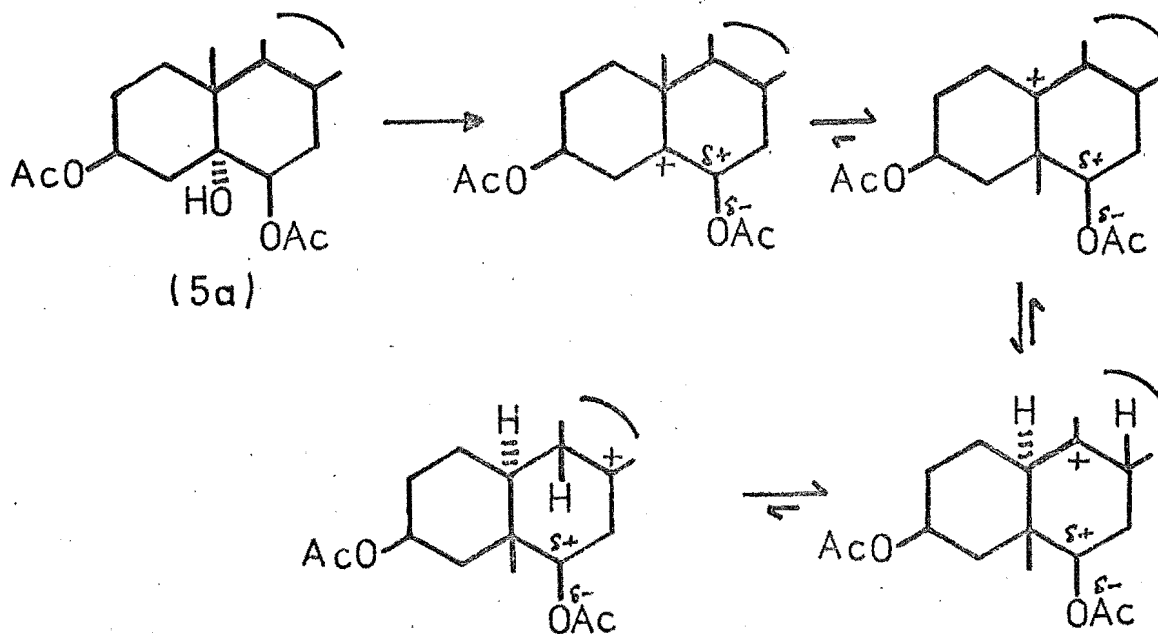
5-Chloro-5 $\alpha$ -cholestane (58) was prepared by bubbling  $\text{HCl}$  gas

through an ether solution of cholest-5-ene (60). A solution of 5-chloro-5 $\alpha$ -cholestane in benzene-methanol was allowed to react with silver oxide. The product mixture was found by n.m.r. to contain cholest-4-ene (59) and cholest-5-ene (60). The specific rotation of this mixture was +29° corresponding to a 7:3 mixture of cholest-4-ene (59) and cholest-5-ene (60). Glc did not show the presence of any other olefin. Reaction of 5-chloro-5 $\alpha$ -cholestane (58) in nitrobenzene, a solvent of higher dielectric constant than benzene, gave essentially the same product composition; cholest-4-ene (67%) and cholest-5-ene (33%). Silver oxide reacts with methanol to form silver hydroxide in low concentration which is sufficiently soluble in benzene and nitrobenzene to effect cleavage of the C-Cl bond of 5-chloro-5 $\alpha$ -cholestane.

The failure of the 5 $\alpha$ -cholestan-5-ol (57a) or 5-chloro-5 $\alpha$ -cholestane to undergo backbone rearrangement suggests that either the carbonium ions formed are not very "hot" or that proton abstraction by some basic species occurs more rapidly than C(10)-methyl migration. This failure of the C(10)-methyl group to migrate indicates that an electron withdrawing substituent at C(4) or C(6) may be essential for skeletal rearrangement to occur. In contrast, 4 $\beta$ -acetoxy-5 $\alpha$ -cholestan-5-ol (26b) with  $\text{H}_2\text{SO}_4\text{-Ac}_2\text{O-AcOH}$  readily rearranged<sup>36</sup> to give 4 $\beta$ -acetoxy-5 $\beta$ -methyl-19-norcholest-9(10)-ene (60%) and 17% of more extensively rearranged products. The separation between the electron withdrawing substituent at C(4) and the carbonium ion intermediates is increased at each successive carbon atom involved in the backbone rearrangement. In contrast, the rearrangement of 3 $\beta$ ,6 $\beta$ -diacetoxy-5 $\alpha$ -cholestan-5-ol (5a) with  $\text{H}_2\text{SO}_4\text{-Ac}_2\text{O-AcOH}$ <sup>12</sup> would involve separation of the developing

carbonium ion from the electron withdrawing substituent at C(6) in rearrangement of the C(5) carbonium ion to C(10) and C(9) carbonium ions. A hydride shift from C(8) to C(9) would result in the formation of a C(8) carbonium ion only two carbons away from the C(6)-acetate (Scheme 17). Migration of hydride from C(8) to C(9) would therefore be unfavourable and it is not surprising to find that rearrangement does not occur past the formation of 3 $\beta$ ,6 $\beta$ -diacetoxy-5 $\beta$ -methyl-19-norcholest-9(10)-ene (6a).

The failure of cholest-5-ene (60) to react with BF<sub>3</sub>.etherate in Ac<sub>2</sub>O under the reaction conditions effective for reaction of the 5 $\alpha$ -acetate (57b) demonstrates that the backbone rearrangement is not occurring via this olefin.



Scheme 17



#### (4) Reactions of 17-Oxygenated Steroids

Changing the substituent at the C(17)-position of a steroid can affect the course of reactions in rings A and B in a marked way as electronic effects are easily transmitted through the molecular skeleton.<sup>61</sup> Peterson<sup>62</sup> calculated that the inductive effect of a remote substituent falls off by a constant factor of 0.51 for each  $\sigma$ -bond between the substituent and the reaction centre when every possible transmission route is summed. Using this method we can calculate that the effect of a C(17)-substituent at C(5) is about 25% of that of the same substituent at C(3). Guest and Marples have recently found that as the inductive withdrawing effect of a substituent at C(17) increases, the reactivity of a 5,6-epoxide with acids decreases.

Backbone rearrangements of steroids involve the development of positive charge at successive carbons of the molecular framework. These carbonium ion intermediates will be affected by a C(17)-substituent. For electron withdrawing substituents, the nearer the carbonium ion to C(17) the greater will be the destabilizing influence of the substituent. It is unusual to find significant spiro rearrangement in compounds containing an electron withdrawing C(17)-substituent. There are, however, a few examples known where significant backbone rearrangement occurs despite the presence of a C(17)-electron withdrawing group. Reaction of 3 $\alpha$ -methylaminoandrost-5-en-17-one (62) with sulphuric acid gave 3 $\alpha$ -methylamino-5 $\beta$ -methyl-19-nor-10 $\alpha$ ,14 $\beta$ -androst-8(9)-en-17-one (63a) (45%) and the 10 $\beta$ -epimer (63b) (55%)<sup>52</sup>. Reaction of 3 $\beta$ -dimethylaminoandrost-5-en-17-one (64) with sulphuric acid gives 3 $\beta$ -dimethylamino-5 $\beta$ -methyl-19-nor-10 $\beta$ ,14 $\beta$ -androst-8(9)-en

17-one (65) (5%) and two 14 $\beta$ -spirans (66) (20%) and (67) (5%)<sup>47</sup>.

9 $\alpha$ ,11 $\alpha$ -Epoxyandrost-4-en-3,17-dione (68) reacts with BF<sub>3</sub> gas to give 11 $\alpha$ -hydroxyandrost-4,8(14)-dien-3,17-dione (69) in 23% yield<sup>40</sup>. In contrast, reactions of the 6 $\beta$ -chloro- and 6 $\beta$ -fluoro- derivatives of 3 $\beta$ -acetoxy-5-hydroxy-5 $\alpha$ -androstan-17-one (70) with H<sub>2</sub>SO<sub>4</sub>-Ac<sub>2</sub>O-AcOH<sup>37</sup> and reactions of 3 $\beta$ -substituted-5,6-epoxyandrostan-17-ones (71) with BF<sub>3</sub>.etherate give no products where backbone rearrangement has occurred past C(9).

In this study we have examined the reaction of 3 $\beta$ ,5 $\alpha$ ,6 $\beta$ -triacetoxy androstan-17-one (72b) with BF<sub>3</sub>.etherate in acetic anhydride.

3 $\beta$ ,6 $\beta$ -Diacetoxy-5-hydroxy-5 $\alpha$ -androstan-17-one (72a) was prepared from dehydroepiandrosterone (73a) by standard procedures. Epoxidation of 3 $\beta$ -acetoxyandrost-5-en-17-one (73b) with m-chloroperbenzoic acid was slow because of the long range inductive effect of the 17-ketone<sup>61</sup>. 3 $\beta$ ,5,6 $\beta$ -Triacetoxy-5 $\alpha$ -androstan-17-one (72a) by reaction with acetic anhydride-perchloric acid-carbon tetrachloride.

The reaction of 3 $\beta$ ,6 $\beta$ -diacetoxy-5-hydroxy-5 $\alpha$ -androstan-17-one (72a) in H<sub>2</sub>SO<sub>4</sub>,AcOH-Ac<sub>2</sub>O was carried out to obtain an authentic sample of 3 $\beta$ ,6 $\beta$ -diacetoxy-5 $\beta$ -methyl-19-norandrost-9(10)-en-17-one (74). (This compound was initially assigned as 3 $\beta$ ,6 $\beta$ -diacetoxy-5 $\beta$ -methyl-19-norandrost-8(9)-en-17-one by Davis and Petrow<sup>64</sup> who also assigned the "Westphalen diacetate" as 3 $\beta$ ,6 $\beta$ -diacetoxy-5 $\beta$ -methyl-19-norcholest-8(9)-ene. They later<sup>65</sup> revised the "Westphalen diacetate" to the correct  $\Delta^{9(10)}$  structure. The  $\Delta^{9(10)}$ -compound (74) was similar (by infra red and n.m.r.) to its 6 $\alpha$ -epimer, 3 $\beta$ ,6 $\alpha$ -diacetoxy-5 $\beta$ -methyl-19-norandrost-9(10)-en-17-one (76) prepared from 3 $\beta$ -acetoxy-5 $\alpha$ ,6 $\alpha$ -epoxyandrostan-17-one.<sup>63</sup>) 3 $\beta$ ,6 $\beta$ -Diacetoxyandrost-4-en-17-one (75) and 3 $\beta$ ,5,6 $\beta$ -triacetoxy-

5 $\alpha$ -androstan-17-one (72b) were also obtained from the reaction of 3 $\beta$ ,6 $\beta$ -diacetoxy-5-hydroxy-5 $\alpha$ -androstan-17-one (72a) with acid. An authentic sample of 3 $\beta$ ,6 $\beta$ -diacetoxyandrost-4-en-17-one (75) was prepared by the reaction of 3 $\beta$ ,6 $\beta$ -diacetoxy-5-hydroxy-5 $\alpha$ -androstan-17-one (72a) with thionyl chloride in pyridine.

The reaction of 3 $\beta$ ,5,6 $\beta$ -triaceoxy-5 $\alpha$ -androstan-17-one (72b) with BF<sub>3</sub>.etherate in acetic anhydride was difficult to carry out. At room temperature no reaction occurred and at higher temperatures a small amount of rearranged steroidal material was obtained but there was a significant quantity of organic tar formed. A compromise temperature of 90° and a time of 20 minutes was selected, giving organic tar (40%), rearranged compounds (29%) and unreacted 3 $\beta$ ,5,6 $\beta$ -triaceoxy-5 $\alpha$ -androstan-17-one (72b) (31%). Of the rearranged products, the compound of lowest polarity was an unidentified aromatic compound isolated in 4% yield. The n.m.r. spectrum showed aromatic protons centred at  $\delta$  7.61 ppm, a triplet at  $\delta$  4.30 ppm and a methyl at  $\delta$  0.93 ppm. Also formed in the reaction were 3 $\beta$ ,6 $\beta$ -diacetoxyandrost-4-en-17-one (75) (4%) and 3 $\beta$ ,6 $\beta$ -diacetoxy-5 $\beta$ -methyl-19-norandrost-9(10)-en-17-one (74) (16%).

The reluctance of 3 $\beta$ ,5,6 $\beta$ -triaceoxy-5 $\alpha$ -androstan-17-one (72b) to undergo reaction with BF<sub>3</sub> demonstrates the suppression of the C(5)-O bond cleavage caused by the inductive effect of the C(17)-ketone. The combined effects of the 3 $\beta$ - and 6 $\beta$ - acetates are known not to suppress C(5)-O bond cleavage. This is evident from the reaction of 3 $\beta$ ,5,6 $\beta$ -triaceoxy-5 $\alpha$ -cholestane (5e) with BF<sub>3</sub>.etherate in benzene which gave 3 $\beta$ ,6 $\beta$ -diacetoxy-5 $\beta$ ,14 $\beta$ -dimethyl-18,19-bisnorcholest-13(17)-ene (7) in 50% yield <sup>16</sup>.

Formation of  $\Delta^{8(14)}$ -olefin from the rearrangement of  $3\beta, 5, 6\beta$ -triacetoxy- $5\alpha$ -androstan-17-one (72b) is not favoured as the  $6\beta$ -acetate and the C(17)-ketone would make carbonium ion formation at C(8) and C(14) unfavourable. It is therefore not surprising that  $3\beta, 6\beta$ -diacetoxy- $5\beta$ -methyl-19-norandrost-9(10)-en-17-one (74) is the most extensively rearranged product formed.

### (5) Synthesis of Unnatural Steroids

To investigate more fully the rearrangements of steroids having cis A/B or cis B/C ring junctions we attempted the synthesis of 4,5-epoxy- and 4-acetoxy-5-oxygenated-  $9\beta$ - and  $10\alpha$ - cholestanes. These compounds were chosen for study as there is extensive information available on reactions of their analogues in the natural steroid series.

Philips Gloeilampenfabrieken<sup>68</sup> prepared  $10\alpha$ -pyrosta-4,22-dien-3-one (82a) from  $10\alpha$ -pyrocalciferol (83a) in an overall yield of 24%. A similar route was used by Williams<sup>69,88</sup> to prepare  $9\beta$ -ergosta-4,22-dien-3-one (84a) from  $9\beta$ -ergosterol (85a). We chose to follow a similar synthetic route, to prepare  $10\alpha$ -cholest-4-ene (86) and  $9\beta$ -cholest-4-ene (87).

Vitamin D<sub>3</sub> (88) was pyrolysed in decalin at 150° under nitrogen in the dark for 2 hours to give  $10\alpha$ -cholesta-5,7-dien-3 $\beta$ -ol (83b) and  $9\beta$ -cholest 5,7-dien-3 $\beta$ -ol (85b)<sup>87</sup>. The  $10\alpha$ -compound (83b) crystallized from light petroleum and was relatively stable but the  $9\beta$ -compound (85b) could be kept for only a few days.  $9\beta$ -Cholesta-5,7-dien-3 $\beta$ -ol (85b) was heated under reflux for 5 hours with aluminium isopropoxide in toluene and cyclohexanone under anhydrous conditions. The product,  $9\beta$ -cholesta-4,7-dien-3-one (89b), was contaminated with a large amount of cyclohexanone polymers which were removed by extensive chromatography. The structure of  $9\beta$ -cholesta-4,7-dien-3-one (89b) was assigned on the basis of the infra-red spectrum ( $\nu_{\text{max}}$  1674) cm<sup>-1</sup> and the ultraviolet spectrum ( $\lambda_{\text{max}}$  244 nm ( $\epsilon$  13,200)). The n.m.r. spectrum showed the C(4)-proton as a singlet at  $\delta$  5.68 and the C(7)-proton as a multiplet centred at  $\delta$  5.52.

10 $\alpha$ -Cholest-5,7-dien-3 $\beta$ -ol (83b) was also reacted with aluminium isopropoxide in toluene and cyclohexanone to give 10 $\alpha$ -cholest-4,7-dien-3-one (90b) contaminated with cyclohexanone polymers. The more volatile of these polymers were removed by steam distillation<sup>68</sup> but the remainder proved impossible to remove since the compound was not stable to chromatography on deactivated alumina, neutral alumina, or silica. The extensive trituration and crystallization procedure employed by Williams<sup>70</sup> to purify 10 $\alpha$ -ergost-4,7,22-trien-3-one (90a) failed to work for this system. As the impurity present in 10 $\alpha$ -cholest-4,7-dien-3-one (90b) inhibited the reaction with HBr in acetic acid, the planned synthetic scheme for the preparation of 10 $\alpha$ -cholest-4-ene (86) was abandoned.

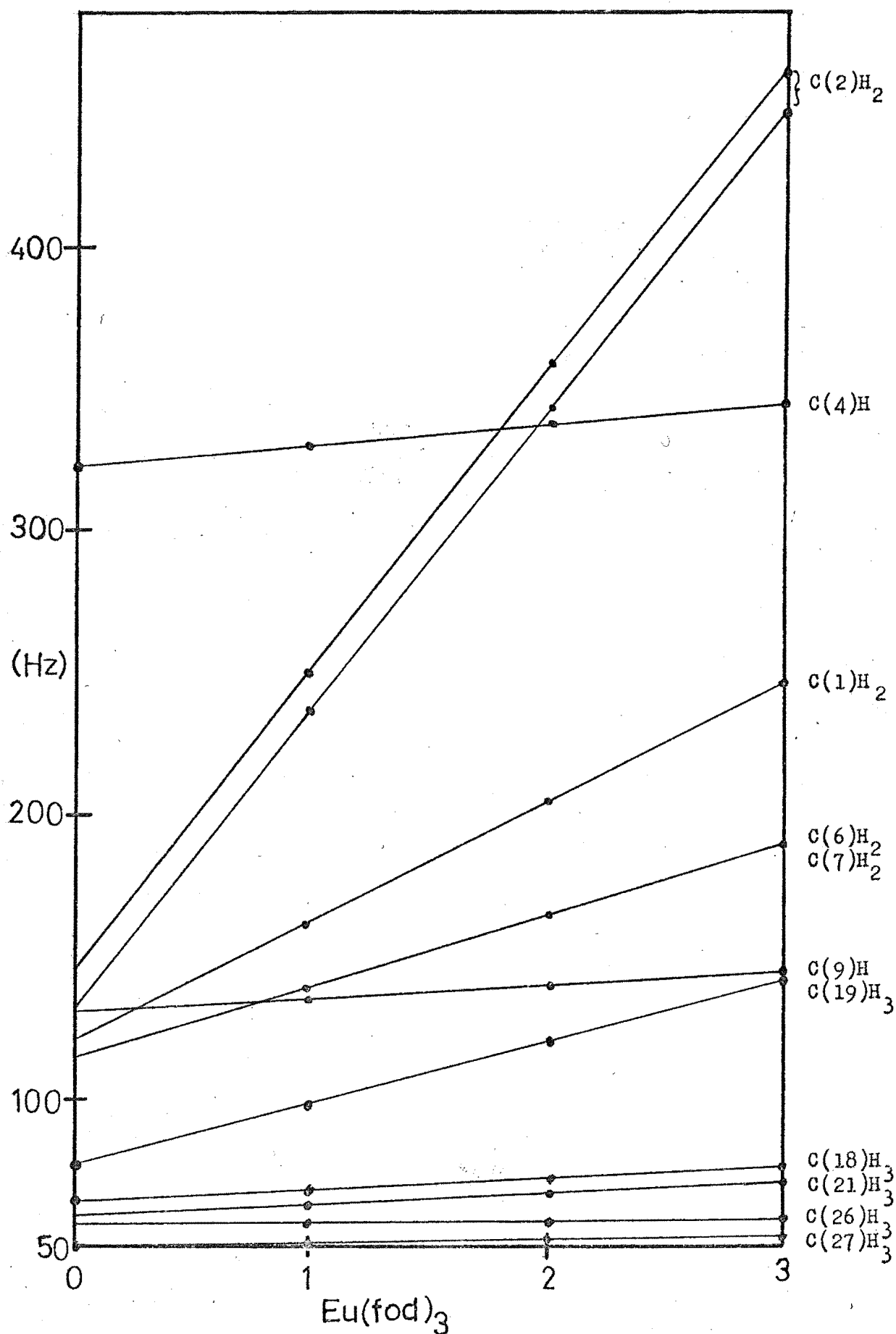
An attempt to prepare 9 $\beta$ -cholest-4,6-dien-3-one (92b) by treatment of 9 $\beta$ -cholest-4,7-dien-3-one (89b) with HBr-acetic acid<sup>85,86</sup> met with limited success. 9 $\beta$ -Cholest-4,8(14)-dien-3-one (91b), isolated in 67% yield was one of the two products formed, and the second, isolated in 20% yield was 8 $\beta$ ,9 $\beta$ -cholest-4,6-dien-3-one (92). The structure of the former compound was assigned from the infrared ( $\nu$  max. 1725 cm<sup>-1</sup>) and the ultraviolet spectra ( $\lambda$  max. 248.5 nm;  $\epsilon$  16,800). Accurate mass measurements on the parent ion showed the molecular formula to be C<sub>27</sub>H<sub>42</sub>O. The positions of the double bonds were determined from the ultraviolet and n.m.r. spectra. The ultraviolet spectrum was consistent with the presence of a conjugated enone chromophore and the n.m.r. showed only one olefinic proton as a singlet at  $\delta$  5.40. From this information and from the molecular formula, the compound was deduced to possess a tetrasubstituted double bond. The C(18)H<sub>3</sub> resonance was deshielded from  $\delta$  0.57 in

the  $\Delta^{4,7}$ -3-one (89b) to  $\delta$  0.83 indicating that the olefinic bond was in a position to deshield the C(18)H<sub>3</sub>. Application of the shift reagent Eu(fod)<sub>3</sub> coupled with double resonance experiments (Figure 5) indicated the C(20)-proton was not allylic, and thus the double bond is not  $\Delta^{13,17}$ . The structure was assigned as 9 $\beta$ -cholest-4,8(14)-dien-3-one (91b). In natural steroids an 8(14)-double bond deshields the C(18)H<sub>3</sub> and models of this 9 $\beta$ -compound (91b) indicate the same to be true. Isomerisation of  $\Delta^7$ -olefins to the  $\Delta^{8(14)}$  position with HBr in acetic acid is not unprecedented. 5 $\alpha$ ,9 $\beta$ ,10 $\alpha$ -Luminost-7,22-dien-3 $\beta$ -ol isomerises to 5 $\alpha$ ,9 $\beta$ ,10 $\alpha$ -luminost-8(14),22-dien-3 $\beta$ -ol under these reaction conditions <sup>71</sup>.

The second dienone was assigned as 8 $\beta$ ,9 $\beta$ -cholest-4,6-dien-3-one (92b) on the following evidence:- the infrared spectrum shows a carbonyl absorption at 1668 cm<sup>-1</sup> and weak olefinic absorptions at 1623 and 1588 cm<sup>-1</sup>. The n.m.r. spectrum showed the C(4)-proton as a singlet at  $\delta$  5.72 ppm and both the C(6)- and C(7)- protons as multiplets centred at  $\delta$  6.03 ppm. The ultraviolet absorption maximum at 285.5 nm was weak ( $\epsilon$  1,800) and suggests the dienone chromophore is twisted.

Protonation of the  $\Delta^7$ -olefin bond in 9 $\beta$ -cholest-4,7-dien-3-one (89b) can occur from either the  $\alpha$ - or the  $\beta$ - face. Dreiding models for 8 $\beta$ ,9 $\beta$ -cholest-4,6-dien-3-one (92b) show that a planar arrangement for the dienone chromophore is only possible if ring C is in a boat conformation. If this compound is in the more stable conformation with ring C as a chair, a dihedral angle of 30° results between the  $\Delta^4$ - and  $\Delta^6$ - olefin bonds, and this would explain the low ultraviolet extinction coefficient. Models of the isomeric compound having the

Figure 5. Changes in the Chemical Shifts of Protons in  $9\beta$ -Cholesta-4,8(14)-dien-3-one on Adding  $\text{Eu}(\text{fod})_3$ .





8 $\alpha$ -configuration, 8 $\alpha$ ,9 $\beta$ -cholesta-4,6-dien-3-one indicate that a conformation with ring B as a semi-boat and ring C as a boat would be the most stable. Such a conformation also results in a dihedral angle of 40° between the  $\Delta^4$ - and  $\Delta^6$ - bonds. Acid-catalysed isomerisations of olefins have generally been observed to lead to the thermodynamically most stable olefin.<sup>66,86</sup> The assignment of configuration at C(8) of dienone (92b) rests on the greater thermodynamic stability of this compound compared with the 8 $\alpha$ -epimer. In the 8 $\beta$ -epimer ring B and ring C are in half-chair conformations respectively while for the 8 $\alpha$ -epimer ring B and ring C are in a half-boat and boat conformation respectively. The stereochemistry at C(8), however, cannot be known for certain. Williams<sup>73</sup> in his study of the reaction of 9 $\beta$ -ergosta-4,7,22-trien-3-one (89a) with HCl/methanol assigned one of the two reaction products as 8 $\beta$ ,9 $\beta$ -ergosta-4,6,22-trien-3-one (92a) on a similar thermodynamic argument. The other product was not identified, but it is possible that it is 9 $\beta$ -ergosta-4,8(14),22-trien-3-one (91a).

The synthetic scheme for the preparation of 4,5-epoxy- and 4-acetoxy-5-hydroxy- 9 $\beta$ -cholestanes was to involve hydrogenation of 9 $\beta$ -cholesta-4,6-dien-3-one (92b) with palladium on charcoal. The scheme, however, failed since 9 $\beta$ -cholesta-4,6-dien-3-one could not be prepared in quantities sufficient to continue the sequence. Hydrogenation of 9 $\beta$ -cholesta-4,8(14)-dien-3-one (91b) and 9 $\beta$ -cholesta-4,7-dien-3-one (89b) was attempted to try and find an alternative synthetic route to 9 $\beta$ -cholest-4-ene (87). Hydrogenation of 9 $\beta$ -cholest 4,8(14)-dien-3-one (91b) under high pressure (105 atmospheres),

catalysed by palladium on charcoal gave 5 $\xi$ ,9 $\beta$ -cholest-8(14)-en-3-one (93). The n.m.r. and i.r. spectra showed that the  $\Delta^4$ -olefinic bond had been reduced and the presence of the  $\Delta^{8(14)}$ -olefinic bond was deduced from the bright colour that formed on addition of tetranitromethane. Hydrogenation of 9 $\beta$ -cholesta-4,7-dien-3-one (89b) under similar reaction conditions gave 5 $\xi$ ,9 $\beta$ -cholest-7-en-3-one (94). 9 $\beta$ -Cholesta-4,7-dien-3-one (89b) was also hydrogenated at high pressure (65 atmospheres) and at a temperature of 100° using Adam's catalyst (PtO<sub>2</sub>) to give 5 $\xi$ ,8 $\xi$ ,9 $\beta$ -cholestan-3 $\xi$ -ol (95). Oxidation of this compound gave 5 $\xi$ ,8 $\xi$ ,9 $\beta$ -cholestan-3-one (96). The stereochemistry at C(5) and C(8) are not known and tlc shows the compound to be impure. Because of these difficulties the synthetic scheme was discontinued.

### CONCLUSION

The reactions of 5- hydroxy- and acetoxy- cholestanes with  $\text{H}_2\text{SO}_4\text{-Ac}_2\text{O-AcOH}$  and  $\text{BF}_3\text{.etherate-Ac}_2\text{O}$  respectively are best rationalised in terms of discrete carbonium ion intermediates. The initial conformation of the C(5)-carbonium ion will be dependent on substituent effects and the most favoured leaving path for the departing entity. This carbonium ion is thought to undergo conformational changes at rates comparable with other reaction processes, e.g., elimination and methyl migration.

We have shown that reaction of  $3\beta,6\beta$ -diacetoxy- $5\alpha$ -cholestan-5-ol (5a) and  $4\beta$ -acetoxy- $5\alpha$ -cholestan-5-ol (26b) with  $\text{H}_2\text{SO}_4\text{-Ac}_2\text{O-AcOH}$  does not proceed by a "stop-start" mechanism involving olefin or cyclopropane intermediates. The mechanism of backbone rearrangement under the conditions described involves a series of rapidly equilibrating carbonium ion intermediates. The reaction sequence is terminated by the abstraction of a proton from these carbonium ion intermediates with consequent formation of products.

The failure of  $3\beta$ -substituted- $5\alpha$ -cholestan-5-ols and  $5\alpha$ -cholestan-5-ol (57a) on reaction with  $\text{H}_2\text{SO}_4\text{-Ac}_2\text{O-AcOH}$  to give rearrangement products, suggests either that electron withdrawing substituents on carbons near C(5) are necessary before rearrangement can occur, or that basic species present in the reaction system abstract hydrogen before rearrangement can occur. Backbone rearrangement products are however obtained from reactions of 3-substituted- $5\alpha$ -fluorocholestanes and 3-substituted- $5\alpha$ -acetoxycholestanes with  $\text{BF}_3\text{.etherate}$  in  $\text{Ac}_2\text{O}$ .

The reluctance of  $3\beta,5\alpha,6\beta$ -triacetoxyandrostan-17-one (72b) to react with  $\text{BF}_3\text{.etherate-Ac}_2\text{O}$  demonstrates that the C(17)-ketone suppresses C(5)-O bond heterolysis.

### EXPERIMENTAL

Melting points are uncorrected. Optical rotations were determined for  $\text{CHCl}_3$  solutions. Infrared spectra were recorded on a Shimadzu IR27G spectrophotometer, as KBr discs or solutions in  $\text{CCl}_4$  or  $\text{CS}_2$ . Ultraviolet absorptions were measured on a Shimadzu MPS-50L for methanol or trifluoroethanol solutions. N.m.r. spectra were recorded on a Varian A60 or T60 spectrometer using  $\text{CDCl}_3$  or  $\text{CCl}_4$  solutions with TMS and  $\text{CHCl}_3$  as internal standards. Mass spectra were recorded on an A.E.I. MS902 spectrometer.

The alumina used for column chromatography was Spence grade H, deactivated by the addition of 10% v/v of 10% acetic acid. Light petroleum refers to the fraction of b.p.  $50-70^\circ$ . All solvents for column chromatography were of purified technical grade. Benzene and light petroleum were distilled off  $\text{P}_2\text{O}_5$ . Ether was distilled off NaH.

Merck silica gel G with binder was used for TLC. Chloroform was the solvent most used for developing chromatograms and the visualizing agent used was phosphomolybdic acid in ethanol.

#### Cholest-4-ene

Cholest-4-en-3-one (77) was prepared by the method of Fieser,<sup>97</sup> m.p.  $75-79^\circ$ ,  $[\alpha]_D + 106^\circ$  (Lit.cit.,<sup>97</sup> m.p.  $81-82^\circ$ ,  $[\alpha]_D + 92^\circ$ ). Reduction with  $\text{NaBH}_4$  in methanol followed by acetylation with  $\text{Ac}_2\text{O}$ -pyridine gave a crude mixture of epimeric 3-acetoxycholest-4-enes. This material was reduced with lithium in liquid  $\text{NH}_3$  and ether and, after purification by chromatography on active alumina, crystallization from methanol-ether gave cholest-4-ene (59), m.p.  $80-82^\circ$ ,  $[\alpha]_D + 68^\circ$  (c, 4.2) (Lit.cit.,<sup>66</sup> m.p.  $83-84^\circ$ ,  $[\alpha]_D + 66^\circ$ ), N.m.r.  $\delta$  5.29

( $\frac{h}{2}$  8Hz; C(4)H), 1.00 (C(19)H<sub>3</sub>), 0.68 (C(18)H<sub>3</sub>), ppm.

#### 4 -Acetoxycholestan-5-ols

A solution of cholest-4-ene (59) (1.4 g), osmium tetroxide (1 g) in pyridine (35 ml) and chloroform (35 ml) was kept at room temperature for 12 days. The resulting osmate esters were reduced with sodium meta bisulphite<sup>93</sup> to give, after chromatography on deactivated alumina (50 g), cholest-4-ene (170 mg), 5 $\alpha$ -cholestan-4 $\alpha$ ,5-diol (32a) (275mg) as needles from methanol, m.p. 114-116°, [ $\alpha$ ]<sub>D</sub> +14° (c, 1.01), (Lit.cit.,<sup>99</sup> m.p. 139-140°, [ $\alpha$ ]<sub>D</sub> +14°),  $\nu_{\max}$ . 3640, 3590 cm<sup>-1</sup>. N.m.r.  $\delta$  3.66 ( $\frac{h}{2}$  17Hz; C(4)H), 0.92 (C(19)H<sub>3</sub>), 0.65 (C(18)H<sub>3</sub>) ppm, and 5 $\beta$ -cholestan-4 $\beta$ ,5-diol (33a) (2.06g) as needles from methanol, m.p. 134-135°, [ $\alpha$ ]<sub>D</sub> +41° (c, 1.6), (Lit.cit.,<sup>99</sup> m.p. 135-136°, [ $\alpha$ ]<sub>D</sub> +25°),  $\nu_{\max}$ . 3520, 3360 cm<sup>-1</sup>. N.m.r.  $\delta$  4.0 ( $\frac{h}{2}$  18Hz; C(4)H), 0.95 (C(19)H<sub>3</sub>), 0.66 (C(18)H<sub>3</sub>) ppm. The diols were acetylated at room temperature and gave, after chromatography to separate the hydroxy-acetates from unreacted starting diols, 4 $\alpha$ -acetoxy-5 $\alpha$ -cholestan-5-ol (32b) as needles from methanol, m.p. 146-148°, [ $\alpha$ ]<sub>D</sub> +45° (c, 2.9), (Lit.cit.,<sup>100</sup> m.p. 149°),  $\nu_{\max}$ . 3626, 1741, 1240 cm<sup>-1</sup>. N.m.r.  $\delta$  4.98 (d, J = 8Hz; C(4)H), 2.04 (OAc), 0.97 (C(19)H<sub>3</sub>), 0.64 (C(18)H<sub>3</sub>), ppm. (Found: C, 78.4; H, 11.3. C<sub>29</sub>H<sub>50</sub>O<sub>3</sub> requires C, 78.0; H, 11.3%) and 4 $\beta$ -acetoxy-5 $\beta$ -cholestan-5-ol (33b) as needles from methanol, m.p. 109-111°, [ $\alpha$ ]<sub>D</sub> +40° (c, 1.8), (Lit.cit.,<sup>100</sup> m.p. 115-117°, [ $\alpha$ ]<sub>D</sub> +31°),  $\nu_{\max}$ . 3630, 1745, 1240 cm<sup>-1</sup>. N.m.r.  $\delta$  5.39 (t, J = 7Hz; C(4)H), 2.07 (OAc), 0.97 (C(19)H<sub>3</sub>), 0.64 (C(18)H<sub>3</sub>) ppm. (Found: C, 78.0; H, 11.5. C<sub>29</sub>H<sub>50</sub>O<sub>3</sub> requires C, 78.0; H, 11.3%).

4 $\alpha$ ,5 $\alpha$ -Diacetoxycholestane

To a solution of 4 $\alpha$ -acetoxy-5 $\alpha$ -cholestan-5-ol (32b) (900 mg) in chloroform (15 ml) was added freshly distilled N,N-dimethylaniline (1.6 ml) and acetyl chloride (1.6 ml) and the mixture heated under reflux for 22 hr. The steroidal material was isolated by means of dichloromethane and, after removal of solvent and crystallization from methanol-ether, gave 4 $\alpha$ ,5 $\alpha$ -diacetoxycholestane (32c) (630 mg) as plates, m.p. 100-103°,  $[\alpha]_D^{25}$  -61° (c, 1.3),  $n_D^{25}$  max. 1739, 1749, 1240 cm<sup>-1</sup>. N.m.r.  $\delta$  5.15 (t, J = 7Hz; C(4)H, 2.08 (C(5)OAc), 2.03 (C(4)OAc), 1.03 (C(19)H<sub>3</sub>), 0.65 (C(18)H<sub>3</sub>) ppm. (Found M<sup>+</sup> 488, (M<sup>+</sup>-60) 428.365540. C<sub>31</sub>H<sub>52</sub>O<sub>4</sub> requires M<sup>+</sup> 488, (M<sup>+</sup>-HOAc) 428.365412). (Found: C, 76.1; H, 10.6. C<sub>31</sub>H<sub>52</sub>O<sub>4</sub> requires C, 76.2; H, 10.7%).

4 $\beta$ ,5-Diacetoxy-5 $\beta$ -cholestane

To a solution of 4 $\beta$ -acetoxy-5 $\beta$ -cholestan-5-ol (33b) (376 mg) in carbon tetrachloride (25 ml) was added acetic anhydride (2.5 ml) and perchloric acid (0.1 ml) and the mixture kept at room temperature for 10 mins. The steroidal material was isolated by means of ether and adsorbed onto deactivated alumina (2.5 g). Elution with light petroleum-benzene (4:1) gave 4 $\beta$ ,5-diacetoxy-5 $\beta$ -cholestane (33c) as a gum,  $[\alpha]_D^{25}$  +16° (c, 1.5),  $n_D^{25}$  max. 1743 (broad), 1240 cm<sup>-1</sup>. N.m.r.  $\delta$  5.52 (t, J = 7Hz; C(4)H), 2.03 (C(4)OAc, C(5)OAc), 0.97 (C(19)H<sub>3</sub>), 0.64 (C(18)H<sub>3</sub>) ppm. (Found: M<sup>+</sup> 488, (M<sup>+</sup>-60) 428.365114. C<sub>31</sub>H<sub>52</sub>O<sub>4</sub> requires M<sup>+</sup> 488, (M<sup>+</sup>-HOAc) 428.365412).

5 $\alpha$ -Cholestan-4 $\beta$ ,5-diol

To a solution of cholest-4-ene (20 g) in ether was added a solution of monoperoxyphthalic acid (18 g) in ether (60 ml) and the mixture stirred at room temperature for 20 hours, giving a crude mixture of epimeric 4,5-epoxycholestanes (27 g). This material was dissolved in dioxane (350 ml) containing perchloric acid (60% aqueous, 2.5 ml) and water (70 ml), and stirred at room temperature for 18 hr. The steroidal material was isolated by means of ether and adsorbed on to deactivated alumina (400 g). Elution with light petroleum gave the epimeric mixture of 4,5-epoxycholestanes (4.9 g) and elution with ether gave 5 $\alpha$ -cholestan-4 $\beta$ ,5-diol (26a) (12 g) as small cubes from ether-methanol, m.p. 169-170°,  $[\alpha]_D +36^\circ$ , (Lit.cit.,<sup>101</sup> m.p. 171-172°,  $[\alpha]_D +27^\circ$ ),  $\nu_{\max}$ . 3450, 3500  $\text{cm}^{-1}$ . N.m.r.  $\delta$  3.54 ( $\text{W}_{\frac{h}{2}}$  5Hz; C(4)H), 1.59 (OH), 1.17 (C(19)H<sub>3</sub>), 0.65 (C(18)H<sub>3</sub>) ppm.

5-Hydroxy-5 $\alpha$ -cholestan-4-one

To a solution of 5 $\alpha$ -cholestan-4 $\beta$ ,5-diol (12 g) (26a) in pyridine (100 ml) was added a solution of chromium trioxide (12 g) in pyridine (120 ml) and the mixture stirred at room temperatures for 13 hr. The solvent was removed in vacuo and the steroidal material isolated by means of pentane and adsorbed onto deactivated alumina (600 g). Elution with benzene gave 5-hydroxy-5 $\alpha$ -cholestan-4-one (78) (7.4 g) as plates from light petroleum, m.p. 159-160°,  $[\alpha]_D +57^\circ$ , (Lit.cit.,<sup>105</sup> m.p. 159°,  $[\alpha]_D +55^\circ$ ),  $\nu_{\max}$ . 3610, 1719  $\text{cm}^{-1}$ . N.m.r.  $\delta$  0.80 (C(19)H<sub>3</sub>), 0.65 (C(18)H<sub>3</sub>) ppm.

Cholest-5-en-4-one

Thionyl chloride (30 ml) was added to a solution of 5-hydroxy-5 $\alpha$ -cholestan-4-one (78) (6.2 g) in dry pyridine (200 ml) cooled in a dry ice-chloroform bath. The mixture was left cold for 20 min then gradually warmed until a red colour developed. Isolation of the steroidal material and chromatography on deactivated alumina (10 g) gave, on elution with light petroleum, cholest-5-en-4-one (79) (3.1 g) as plates from methanol, m.p. 110-111°,  $[\alpha]_D -53.5^\circ$ , (Lit.cit.,<sup>40</sup> m.p. 111°,  $[\alpha]_D -34^\circ$ ),  $\lambda_{\max}$ . 235 nm ( $\epsilon$  7090),  $\nu_{\max}$ . 1692, 1632  $\text{cm}^{-1}$ . N.m.r.  $\delta$  6.41 (q,  $J = 4.8\text{Hz}$ ,  $J' = 2\text{Hz}$ ; C(6)H), 0.97 (C(19)H<sub>3</sub>), 0.70 (C(18)H<sub>3</sub>) ppm.

4 $\alpha$ -Hydroxycholest-5-ene

Lithium aluminium hydride (4.0 g) was added to a solution of cholest-5-en-4-one (79) (4.0 g) in sodium dried ether (300 ml) and refluxed for 30 minutes. The steroidal material was isolated by means of ether and adsorbed onto deactivated alumina (60 g). Elution with light petroleum gave 4 $\alpha$ -hydroxycholest-5-ene (34a) as needles from methanol, m.p. 134-137°, (Lit.cit.,<sup>100</sup> 143-144°),  $\nu_{\max}$ . 3635  $\text{cm}^{-1}$ . N.m.r.  $\delta$  5.67 ( $\text{W}_{\frac{h}{2}} 10\text{z}$ ; C(6)H), 4.18 ( $\text{W}_{\frac{h}{2}} 19\text{Hz}$ ; C(4)H), 2.0 (OH), 0.98 (C(19)H<sub>3</sub>), 0.67 (C(18)H<sub>3</sub>) ppm.

5 $\alpha$ ,6 $\alpha$ -Epoxycholestan-4 $\alpha$ -ol

To a solution of 4 $\alpha$ -hydroxycholest-5-ene (34a) (3.1 g) in sodium dried ether (150 ml) was added m-chloroperbenzoic acid (2 g) and the mixture stirred at room temperature for 19 hr. Removal of the



unreacted peracid and solvent evaporation gave a mixture of epimeric 5,6-epoxycholestan-4 $\alpha$ -ols which was adsorbed onto deactivated alumina (200 g). Elution with light petroleum-ether (9:1) gave 5 $\alpha$ ,6 $\alpha$ -epoxycholestan-4 $\alpha$ -ol (80) (2.2 g) as needles from methanol, m.p. 130-132°, (Lit.cit.,<sup>100</sup> 128-131°),  $\nu_{\text{max}}$ . 3420, 3470  $\text{cm}^{-1}$ . N.m.r.  $\delta$  3.91 (t,  $J = 10\text{Hz}$ ; C(4)H), 3.41 (d,  $J = 4.1\text{ Hz}$ ; C(6)H), 3.36 (OH), 1.01 (C(19)H<sub>3</sub>), 0.61 (C(18)H<sub>3</sub>) ppm. Further elution with light petroleum-ether (9:1-8:2) gave 5 $\beta$ ,6 $\beta$ -epoxycholestan-4 $\alpha$ -ol (81), m.p. 105-108°,  $\nu_{\text{max}}$ . 3461  $\text{cm}^{-1}$ . N.m.r.  $\delta$  4.0 ( $W_{\frac{h}{2}} 16\text{Hz}$ ; C(4)H), 3.62 (d,  $J = 2.1\text{ Hz}$ ; C(6)H), 2.22 (OH), 1.81 (C(19)H<sub>3</sub>), 0.65 (C(18)H<sub>3</sub>) ppm.

#### 5 $\alpha$ -Cholesta-4 $\alpha$ ,5-diol

To a solution of 5 $\alpha$ ,6 $\alpha$ -epoxycholestan-4 $\alpha$ -ol (80) (2.7 g) in dry ether (200 ml) was added lithium aluminium hydride (2 g) and the mixture refluxed for 1 hr. Isolation of the steroid by means of ether gave 5 $\alpha$ -cholesta-4 $\alpha$ ,5-diol (32a) (2.0 g) identical to that prepared by reacting OsO<sub>4</sub> with cholest-4-ene.

#### 4 $\alpha$ -Acetoxy-5 $\alpha$ -cholestan-5-ol-6 $\beta$ -d

To a solution of 5 $\alpha$ ,6 $\alpha$ -epoxycholestan-4 $\alpha$ -ol (80) (66 mg) in dry tetrahydrofuran (10 ml) was added lithium aluminium deuteride (50 mg) and the mixture heated under reflux conditions for 22 hr. The steroidal material was isolated by means of ether to give 5 $\alpha$ -cholestan-4 $\alpha$ ,5-diol-6 $\beta$ -d shown by mass spectrometry to be 95 ( $\pm 5$ )% isotopically pure. The crude diol in pyridine (5 ml) and acetic

anhydride (0.15 ml) was heated at  $80^{\circ}$  for 1 hr and then left for 12 hr at room temperature. The steroidal material, isolated using ether gave 4 $\alpha$ -acetoxy-5 $\alpha$ -cholestan-5-ol-6 $\beta$ -d (37) as plates from methanol-ether, m.p.  $147-149^{\circ}$ , m.m.p. (with unlabelled authentic sample)  $149-150^{\circ}$ .

Reaction of 4 $\alpha$ -acetoxy-5 $\alpha$ -cholestan-5-ol with  $\text{H}_2\text{SO}_4\text{-Ac}_2\text{O-AcOH}$

To a stirred solution of 4 $\alpha$ -acetoxy-5 $\alpha$ -cholestan-5-ol (32b) (250 mg) in acetic acid (10 ml) and acetic anhydride (1.5 ml) at  $30^{\circ}$  was added a solution of sulphuric acid (0.03 ml, 10% w/v) in acetic acid. After allowing sufficient time for thorough mixing (3 sec.) the mixture was poured into ether-benzene (150 ml, 1:1) and aqueous sodium carbonate (20 ml). After isolation of the steroidal material it was adsorbed onto deactivated alumina (9 g). Elution with light petroleum gave 4 $\alpha$ -acetoxycholest-5-ene (34b) (50 mg) as needles from methanol, m.p.  $117-119^{\circ}$ ,  $[\alpha]_D -16^{\circ}$  (c, 2.8), (Lit.cit.,<sup>100</sup> m.p.  $123^{\circ}$ ),  $\nu_{\text{max}}$  1738,  $1240\text{ cm}^{-1}$ . N.m.r.  $\delta$  5.43 (d, J = 5Hz; C(6)H), 5.32 ( $\text{W}_{\frac{1}{2}}$  10Hz; C(4)H), 2.08 (OAc), 1.03 (C(19)H<sub>3</sub>), 0.67 (C(18)H<sub>3</sub>) ppm. (Found C, 81.3; H, 11.3.  $\text{C}_{29}\text{H}_{48}\text{O}_2$  requires C, 81.3; H, 11.3%). Elution with benzene-light petroleum gave starting alcohol (200 mg).

In a separate experiment under the same reaction conditions but with a longer reaction time (10 sec.), no starting alcohol could be detected, the reaction product being a 3:1 mixture of 4 $\alpha$ - and 4 $\beta$ -acetoxycholest-5-enes as measured by integration of the acetate signals in the n.m.r. spectra.

Reaction of 4 $\alpha$ -acetoxy-5 $\alpha$ -cholestan-5-ol-6 $\beta$ -d with H<sub>2</sub>SO<sub>4</sub>-Ac<sub>2</sub>O-AcOH

To a stirred solution of 4 $\alpha$ -acetoxy-5 $\alpha$ -cholestan-5-ol-6 $\beta$ -d (37) (25 mg) in acetic acid (1.25 ml) and acetic anhydride (0.3 ml) was added a solution of sulphuric acid (0.05 ml, 5% w/v) in acetic acid. The solution after 4 sec. was poured into ether-benzene and aqueous sodium carbonate. After removal of solvent, the residue (21 mg) was shown by n.m.r. to be a 3:1 mixture of the 4 $\alpha$ - and 4 $\beta$ - acetoxy cholest-5-enes (34,35). Mass spectrometry indicated that the deuterium label had been retained predominantly ( $89 \pm 5\%$ ) in the product mixture. The mixed acetoxy-olefins were allowed to react with LiAlH<sub>4</sub> in ether. Isolation with ether gave a mixture of 4 $\alpha$ - and 4 $\beta$ - cholest-5-en-4-ol-6 $\beta$ -d shown by mass spectrometry to be  $84 \pm 4\%$  isotopically pure.

Reaction of 4 $\alpha$ -acetoxycholest-5-ene with H<sub>2</sub>SO<sub>4</sub>-Ac<sub>2</sub>O-AcOH

A solution of 4 $\alpha$ -acetoxycholest-5-ene (34b) (100 mg) in acetic acid (4.5 ml), acetic anhydride (0.7 ml), and sulphuric acid (0.015 ml, 5.6% w/v in acetic acid) was kept at room temperature for 10 sec. Isolation of the steroidal material by means of ether-benzene gave a mixture of 4 $\alpha$ - and 4 $\beta$ - acetoxycholest-5-ene (68 mg) shown by n.m.r. to be a 3:1 mixture of the epimers.

Reaction of 4 $\beta$ -acetoxycholest-5-ene with HBF<sub>4</sub>-Ac<sub>2</sub>O-AcOH

A solution of 4 $\beta$ -acetoxycholest-5-ene (35) (27 mg) in acetic acid (1.8 ml), acetic anhydride (0.6 ml), and hydrofluoroboric acid (0.6 ml, 0.5% in acetic acid) was kept at 20° for 25 min. The steroidal material, isolated using ether-benzene, was shown by n.m.r.

to be a mixture of cholest-3,5-diene (38) (70%), 4 $\alpha$ -acetoxycholest-5-ene (34b) (10%), and 4 $\beta$ -acetoxycholest-5-ene (35) (9%).

Reaction of 4 $\alpha$ -acetoxy-5 $\alpha$ -cholestan-5-ol with thionyl chloride-pyridine

To a stirred solution of 4 $\alpha$ -acetoxy-5 $\alpha$ -cholestan-5-ol (32b) (170 mg) in dry pyridine (15 ml) was added thionyl chloride (0.7 ml) and the mixture kept near freezing in a dry ice-chloroform bath for 10 min. The steroidal material was isolated using ether and adsorbed onto deactivated alumina. Elution with benzene gave 4 $\alpha$ -acetoxycholest-5-ene (34b) (141 mg), m.p. 117-119°,  $[\alpha]_D -16^\circ$ (c, 2.4).

Reaction of 4 $\alpha$ -acetoxy-5 $\alpha$ -cholestan-5-ol-6 $\beta$ -d with thionyl chloride-pyridine.

To a stirred solution of 4 $\alpha$ -acetoxy-5 $\alpha$ -cholestan-5-ol-6 $\beta$ -d (37) (20 mg) in pyridine (1 ml) was added thionyl chloride (0.06 ml) and the mixture kept near freezing in a dry ice-chloroform bath for 10 min. The steroidal material was isolated as above and allowed to react with LiAlH<sub>4</sub> in dry ether under reflux for 2 hr. The product, 4 $\alpha$ -hydroxycholest-5-ene (34a), crystallized as needles from methanol, and was identical to an authentic sample m.p. and m.m.p. 131-134°. Mass spectrometry indicated the product to contain 18.5  $\pm$  1.5% deuterium label.

Reaction of 4 $\beta$ -acetoxy-5 $\alpha$ -cholestan-5-ol with thionyl chloride-pyridine.

To a stirred solution of 4 $\beta$ -acetoxy-5 $\alpha$ -cholestan-5-ol (26b) (200 mg) in dry pyridine (7 ml) was added thionyl chloride (1 ml) and the mixture kept near freezing in a chloroform-dry ice bath for 10 min.

The steroidal material was isolated by means of ether and adsorbed onto deactivated alumina (7 gm). Elution with light petroleum gave 4 $\beta$ -acetoxy-cholest-5-ene (35) (125 mg) as needles from acetone-methanol, m.p. 98-100°,  $[\alpha]_D$  -85° (c, 1.3), (Lit. cit.,<sup>101</sup> m.p. 108°,  $[\alpha]_D$  -70°),  $n_{max}$  1.737, 1670 (weak) cm<sup>-1</sup>. N.m.r.  $\delta$  5.72 (d, J = 3Hz; C(6)H), 5.30 ( $\frac{h}{2}$  5Hz; C(4)H), 2.00 (OAc), 1.12 (C(19)H<sub>3</sub>), 0.67 (C(18)H<sub>3</sub>) ppm. (Found C, 80.8; H, 11.4. C<sub>29</sub>H<sub>48</sub>O<sub>2</sub> requires C, 81.3; H, 11.3%).

Reaction of 4 $\alpha$ ,5-diacetoxy-5 $\alpha$ -cholestane with BF<sub>3</sub>·Et<sub>2</sub>O·Ac<sub>2</sub>O

To a solution of 4 $\alpha$ ,5-diacetoxy-5 $\alpha$ -cholestane (32c) (300 mg) in acetic anhydride (50 ml) was added freshly distilled BF<sub>3</sub>·etherate (0.3 ml) and the solution kept at room temperature for 25 sec. The product mixture was isolated by means of ether-benzene and after removal of solvent was adsorbed onto deactivated alumina (20 g). Elution with light petroleum gave a mixture of cholest-3,5-diene (38) and cholest-4,6-diene (39) (170 mg), m.p. 74-76°,  $[\alpha]_D$  -84° (c, 2.47),  $n_{max}$  1.3040, 1749 cm<sup>-1</sup>,  $\lambda_{max}$  230 nm ( $\epsilon$  19,300), 236.5 nm ( $\epsilon$  21,100), 244.5 nm ( $\epsilon$  13,600). N.m.r.  $\delta$  5.40-6.02 (C(3)H, C(4)H, C(6)H), 0.95 (C(19)H<sub>3</sub>), 0.71 (C(18)H<sub>3</sub>) ppm. Further elution with light petroleum gave 4 $\alpha$ -acetoxycholest-5-ene (34b) (24 mg) and 4 $\beta$ -acetoxycholest-5-ene (35) (20 mg). Elution with light petroleum-benzene (9:1) gave 5 $\alpha$ -cholestan-4-one (40) (20 mg) identical to an authentic sample. Further elution with light petroleum-benzene (9:1) gave unreacted 4 $\alpha$ ,5-diacetoxy-5 $\alpha$ -cholestane (32c) (44 mg).

Reaction of 4 $\beta$ -acetoxy-5 $\beta$ -cholestan-5-ol with H<sub>2</sub>SO<sub>4</sub>-Ac<sub>2</sub>O-AcOH

To a solution of 4 $\beta$ -acetoxy-5 $\beta$ -cholestan-5-ol (33b) (200 mg) in acetic acid (8 ml) and acetic anhydride (2 ml) was added a solution of

sulphuric acid (0.84 ml, 1% w/v) in acetic acid and the reaction mixture kept at room temperature for 30 min. The product was isolated using benzene-ether and adsorbed onto deactivated alumina (20 g). Elution with light petroleum gave 4 $\alpha$ -acetoxycholest-5-ene (34b) (10 mg) m.p. 117-119°, followed by 4 $\beta$ -acetoxycholest-5-ene (35) (12 mg) m.p. 99-100°. Further elution with light petroleum gave 5 $\alpha$ -cholestan-4-one (40) (39 mg), m.p. 97-98°,  $[\alpha]_D +38^\circ$  (c, 0.26), (Lit.cit.,<sup>102,103</sup> m.p. 96-98°),  $[\alpha]_D +30^\circ$ ,  $\nu_{\max}$ . 1716 cm<sup>-1</sup>. N.m.r.  $\delta$  0.73 (C(19)H<sub>3</sub>), 0.65 (C(18)H<sub>3</sub>) ppm (Found M<sup>+</sup> 386.354759. C<sub>27</sub>H<sub>46</sub>O requires M<sup>+</sup> 386.354848). Elution with light petroleum-benzene (19:1) gave 4 $\beta$ ,5-diacetoxy-5 $\beta$ -cholestane (33a) (159 mg) as a gum,  $[\alpha]_D +16^\circ$  (c, 1.5),  $\nu_{\max}$ . 1743 (broad), 1240 cm<sup>-1</sup>. Further elution with ether gave polar products (17 mg).

Reaction of 4 $\beta$ ,5-diacetoxy-5 $\beta$ -cholestane with BF<sub>3</sub>.Et<sub>2</sub>O-Ac<sub>2</sub>O.

To a solution of 4 $\beta$ ,5-diacetoxy-5 $\beta$ -cholestane (33c) (219 mg) in acetic anhydride (35 ml) was added freshly distilled BF<sub>3</sub>.etherate (0.2 ml) and the solution kept at room temperature for 5 min. The isolated product was adsorbed onto deactivated alumina (20 g) and elution with light petroleum gave a mixture of 4 $\alpha$ -acetoxycholest-5-ene (34b) (8 mg), 4 $\beta$ -acetoxycholest-5-ene (35) (24 mg), followed by 5 $\alpha$ -cholestan-4-one (40) (47 mg). Elution with ether gave a mixture of polar products (26 mg).

Reaction of 4 $\beta$ -acetoxy-5 $\alpha$ -cholestan-5-ol with H<sub>2</sub>SO<sub>4</sub>-DOAc-Ac<sub>2</sub>O.

To a stirred solution of 4 $\beta$ -acetoxy-5 $\alpha$ -cholestan-5-ol (26b) (243 mg) in DOAc ( >98%<sub>d</sub><sub>1</sub>; containing a 20% excess of Ac<sub>2</sub>O; 27 ml)

and sodium dried acetic anhydride (5 ml) was added a solution of sulphuric acid (0.5 ml; 1% w/v in acetic anhydride) and the mixture left at room temperature for 2 hr. The steroidal material was isolated using ether-benzene (1:1) and adsorbed onto deactivated alumina (30 g). Elution with light petroleum gave 4 $\beta$ -acetoxy-5 $\beta$ -methyl-19-norcholest-9(10)-ene (29) identical to an authentic sample prepared as in the literature.<sup>36</sup>  $M^+ 428$  ( $C_{29}H_{48}O_2$ ),  $M^+:(M^++1) = 100:32$ ,  $(M^+-60+1) = 100:34$ . Further elution gave a mixture of 4 $\beta$ -acetoxy-5 $\beta$ -methyl-19-norcholest-9(10)-ene (29) and 4 $\beta$ -acetoxy-5 $\beta$ -methyl-19-norcholest-8(14)-ene (30). From this mixture the  $\Delta^{8(14)}$ -olefin (30) was separated by preparative tlc on silica,  $M^+ 428$  ( $C_{29}H_{48}O_2$ ),  $M^+:(M^++1) = 100:34$ ,  $(M^+-60):(M^+-60+1) = 100:31$ . Elution with benzene gave a mixture of 4 $\beta$ -acetoxy-5 $\beta$ ,14 $\beta$ -dimethyl-18,19-bisnorcholest-13(17)-ene (31) and 5 $\alpha$ -cholestan-4-one (40),  $\nu_{max}$  1715  $cm^{-1}$ . Preparative tlc gave the  $\Delta^{13(17)}$ -olefin (31) contaminated with a trace of 5 $\alpha$ -cholestan-4-one (40).  $M^+ 428$  ( $C_{29}H_{48}O_2$ ),  $(M^++1) = 100:30$ ,  $(M^+-60):(M^+-60+1) = 100:28$ .

Reaction of 3 $\beta$ ,6 $\beta$ -diacetoxy-5 $\alpha$ -cholestan-5-ol with  $H_2SO_4$ -DOAc-Ac<sub>2</sub>O.

To a stirred solution of 3 $\beta$ ,6 $\beta$ -diacetoxy-5 $\alpha$ -cholestan-5-ol (5a) (108 mg) in acetic acid-d<sub>4</sub> (>98% d<sub>4</sub>; 4 ml) and acetic anhydride (0.9 ml) was added a solution of sulphuric acid (0.1 ml; 8.5% w/v in acetic anhydride) and the mixture stirred at room temperature for 1½ hr. Isolation using ether-benzene (1:1) gave 3 $\beta$ ,6 $\beta$ -diacetoxy-5 $\beta$ -methyl-19-norcholest-9(10)-ene (69) as cubes from methanol identical to an authentic sample prepared using acetic acid-d<sub>6</sub> m.p. 125-126°,  $\nu_{max}$  1730  $cm^{-1}$ ,  $M^+ 426$  ( $C_{31}H_{48}O_4$ -HOAc),  $(M^+-60):(M^+-60+1) = 100:34$ . The

n.m.r. was identical to the authentic  $d_0$  sample,  $\delta$  5.09 ( $W_{\frac{h}{2}}$  9Hz; C(3)H), 4.78 ( $W_{\frac{h}{2}}$  18Hz; C(6)H), 2.06, 2.02 (C(3)OAc, C(6)OAc), 1.21 (C(5 $\beta$ )CH<sub>3</sub>), 0.80 (C(18)H<sub>3</sub>) ppm.

#### Cholest-5-ene

3 $\beta$ -Chlorocholest-5-ene was prepared from cholesterol using thionyl chloride in pyridine. Reduction using lithium in liquid ammonia gave, after chromatography on active alumina, cholest-5-ene (60) as plates from ethanol-ether, m.p. 92-93° (Lit.cit.,<sup>106</sup> m.p. 92-95°). N.m.r.  $\delta$  5.24 (d, J = 4Hz; C(6)H), 0.98 (C(19)H<sub>3</sub>), 0.67 (C(18)H<sub>3</sub>) ppm.

#### 5 $\alpha$ -Cholestan-5-ol

Monoperoxyphthalic acid (2 molar excess) was reacted with a solution of cholest-5-ene (60) (21 g) in dry ether (100 ml) for 2 days at 4°. Isolation of the steroidal material using ether followed by repeated crystallization from acetone gave 5 $\alpha$ ,6 $\alpha$ -epoxycholestane as plates, m.p. 76-78°. N.m.r.  $\delta$  2.87 (d, J = 4Hz; C(6)H), 1.03 (C(19)H<sub>3</sub>), 0.60 (C(18)H<sub>3</sub>) ppm. Reduction of this compound with LiAlH<sub>4</sub> (500 mg) in dry ether (50 ml) gave, after isolation with ether, 5 $\alpha$ -cholestan-5-ol (57a) (708 mg) as small stars from aqueous methanol, m.p. 105-107°, (Lit.cit.,<sup>104</sup> 104-105°),  $\nu$  max. 3630 cm<sup>-1</sup>. N.m.r.  $\delta$  1.37 (OH), 0.95 (C(19)H<sub>3</sub>), 0.64 (C(18)H<sub>3</sub>) ppm. (Found: M<sup>+</sup> 388, (M<sup>+</sup>-18) 370.360190. C<sub>27</sub>H<sub>48</sub>O requires M<sup>+</sup> 388, (M<sup>+</sup>-H<sub>2</sub>O) 370.359934).

#### 5-Acetoxy-5 $\alpha$ -cholestane

A solution of 5 $\alpha$ -cholestan-5-ol (57a) (170 mg) in chloroform (25 ml), acetylchloride (1.5 g), and dimethyl aniline (1.6 g) was



refluxed for 48 hr. After isolation by means of ether, the steroidal material was adsorbed onto 5% deactivated alumina. Elution with light petroleum gave a mixture of cholest-4-ene and cholest-5-ene (76 mg). Elution with light petroleum-benzene gave 5-acetoxy-5 $\alpha$ -cholestane (57b) (51 mg) as needles from ethanol, m.p. 106-108°,  $[\alpha]_D^{25} +31.5^\circ$  (c, 1.6),  $\nu_{\max} 1729 \text{ cm}^{-1}$ . N.m.r.  $\delta$  2.07 (OAc), 0.95 (C(19)H<sub>3</sub>), 0.65 (C(18)H<sub>3</sub>) ppm. (Found: C, 80.9; H, 11.5. C<sub>29</sub>H<sub>50</sub>O<sub>2</sub> requires C, 80.9; H, 11.7%). Elution with benzene gave unreacted 5 $\alpha$ -cholestan-5-ol (57a) (42 mg).

#### 5-Chloro-5 $\alpha$ -cholestane

Hydrogen chloride gas was bubbled through a stirred solution of cholest-5-ene (60) (1 g) in dry ether (100 ml) for 4 hr at room temperature, then the solution left for a further 1½ hr. Evaporation of the solvent in vacuo gave 5-chloro-5 $\alpha$ -cholestane (58) (700 mg) as small stars from methanol-ether, m.p. 94-95°,  $[\alpha]_D^{25} +4.50$  (c, 2.57), (Lit.cit.,<sup>60</sup> m.p. 97°,  $[\alpha]_D^{25} +4.70$ ),  $\nu_{\max} 733 \text{ cm}^{-1}$ <sup>98</sup>. N.m.r.  $\delta$  1.03 (C(19)H<sub>3</sub>), 0.65 (C(18)H<sub>3</sub>) ppm. (Found: M<sup>+</sup> 407.341956. C<sub>27</sub>H<sub>48</sub>Cl requires M<sup>+</sup> 407.344436).

#### Reaction of 5 $\alpha$ -cholestan-5-ol with H<sub>2</sub>SO<sub>4</sub>-Ac<sub>2</sub>O-AcOH.

To a solution of 5 $\alpha$ -cholestan-5-ol (57a) (100 mg) in acetic acid (4 ml) and acetic anhydride (1 ml) was added a solution of sulphuric acid (1 ml, 1% w/v) in acetic acid, and the reaction mixture stirred at room temperature for 20 sec. Isolation by means of ether gave a crystalline mixture of cholest-4-ene (70%) and cholest-5-ene (30%),  $[\alpha]_D^{25} +29^\circ$ . N.m.r.  $\delta$  5.27 (W<sub>2</sub><sup>h</sup> 8Hz; C(4)H and C(6)H), 0.99 C(19)H<sub>3</sub>, 0.68 (C(18)H<sub>3</sub>) ppm. High pressure liquid chromatography showed a trace of an unidentified olefin, possibly 5 $\beta$ ,14 $\beta$ -dimethyl-18,19-

bisnorcholest-13(17)-ene (61).

Reaction of 5-acetoxy-5 $\alpha$ -cholestane with  $\text{BF}_3 \cdot \text{Et}_2\text{O} \cdot \text{Ac}_2$ .

To a solution of 5-acetoxy-5 $\alpha$ -cholestane (57b) (105 mg) in dry acetic anhydride (16 ml) was added freshly distilled  $\text{BF}_3$  etherate (0.16 ml) and the mixture stirred at room temperature for 60 sec. Isolation of the steroidal material using ether gave an oil (95 mg), shown by g.l.c. on 2% SE30 to contain cholest-4-ene (59) and cholest-5-ene (60) (67%) and 5 $\beta$ ,14 $\beta$ -dimethyl-18,19-bisnorcholest-13(17)-ene (61) (33%). Separation of the latter compound was shown to be possible by h.p.l.c. N.m.r.  $\delta$  5.25 ( $\text{W}_{\frac{1}{2}}$  8 Hz: C(4)H and C(6)H), 1.01 (C(19)H<sub>3</sub>), 0.95 (d, J = 7 Hz; C(21)H<sub>3</sub>), 0.88 (14 $\beta$ -CH<sub>3</sub>), 0.83 (d, J = 6 Hz; C(26)H<sub>3</sub>, C(27)H<sub>3</sub>), 0.82 (C(5 $\beta$ )CH<sub>3</sub>), 0.68 (C(18)H<sub>3</sub>) ppm.

Reaction of 5-chloro-5 $\alpha$ -cholestane with  $\text{Ag}_2\text{O} \cdot \text{MeOH} \cdot \text{C}_6\text{H}_6$ .

A solution of 5-chloro-5 $\alpha$ -cholestane (58) (50 mg) in benzene (2 ml) and methanol (0.25 ml) was shaken with silver oxide (45 mg) at room temperature for 5 hr. Isolation of the steroidal material using ether gave a crystalline mixture of cholest-4-ene (70%) and cholest-5-ene (30%),  $[\alpha]_D +29^\circ$  (c, 2.4).

Reaction of 5-chloro-5 $\alpha$ -cholestane with  $\text{Ag}_2\text{O} \cdot \text{MeOH}$ -nitrobenzene.

A solution of 5-chloro-5 $\alpha$ -cholestane (58) (50 mg) in nitrobenzene (2 ml) and methanol (0.25 ml) was stirred rapidly with silver oxide (44 mg) at room temperature for 4 $\frac{1}{2}$  hr. The steroidal material was isolated using ether and adsorbed onto active alumina (2 g). Elution with light petroleum gave a crystalline material (37 mg) containing cholest-4-ene (59) (67%) and cholest-5-ene (60) (33%),  $[\alpha]_D +26^\circ$ .

Attempted reaction of cholest-5-ene with  $\text{BF}_3 \cdot \text{Et}_2\text{O} \cdot \text{Ac}_2\text{O}$ .

To a solution of cholest-5-ene (60) (100 mg) in acetic anhydride (30 ml) was added freshly distilled  $\text{BF}_3$ .etherate (0.15 ml) and the mixture stirred at  $45^\circ$  for 60 sec. Isolation of the steroidal material using ether gave only unreacted cholest-5-ene (60).

Reaction of cholest-5-ene with  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  in  $\text{Ac}_2\text{O} \cdot \text{AcOH}$ .

To a stirred solution of cholest-5-ene (60) (252 mg) in acetic anhydride (40 ml) and acetic acid (0.12 ml) was added freshly distilled boron trifluoride etherate (0.40 ml) and the mixture kept at  $100^\circ$  for 2 hr. Chromatography of the steroidal material, isolated by means of ether, on active alumina (10 g) gave on elution with light petroleum, an oil (225 mg). N.m.r. showed  $5\beta, 14\beta$ -dimethyl-18,19-bisnorcholest-13,17-ene (61) to be the major product (ca 70%),  $\delta$  0.94 (d,  $J = 7\text{Hz}$ ; decoupled by double irradiation at  $-88\text{Hz}$ ;  $\text{C}(21)\text{H}_3$ ), 0.88 ( $\text{C}(14\beta)$ -methyl), 0.85 (d,  $J = 8\text{Hz}$ ;  $\text{C}(26)\text{H}_3$ ,  $\text{C}(27)\text{H}_3$ ), 0.83 ( $\text{C}(5\beta)$ -methyl) ppm. The n.m.r. spectra indicated that at least two other olefins were present ( $\delta$  0.68 and 0.70 ( $\text{C}(18)\text{H}_3$ 's)).

$3\beta$ -Acetoxyandrost-5-en-17-one.

To a solution of dehydroepiandrosterone (73a) (26 g) in dry pyridine (130 ml) was added acetic anhydride (26 ml) and the mixture left at room temperature for 12 hr. Isolation of the steroid using ether gave  $3\beta$ -acetoxyandrost-5-ene (73b) (22 g) as needles from methanol, m.p.  $163\text{--}164^\circ$ , (Lit.cit.,<sup>94</sup>  $164\text{--}165^\circ$ ),  $\nu_{\text{max}}$  1730,  $1240\text{ cm}^{-1}$ .

3 $\beta$ ,6 $\beta$ -Diacetoxy-5 $\alpha$ -hydroxyandrostan-17-one

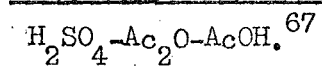
To a solution of 3 $\beta$ -acetoxyandrost-5-en-17-one (73b) (9 gm) in ether (180 ml) was added *m*-chloroperbenzoic acid (6.12 g) and the mixture stirred at room temperature for 1 day. Isolation using ether gave a crude epimeric mixture of 3 $\beta$ -acetoxy-5,6-epoxyandrostan-17-ones (6 g). This crude material was dissolved in acetone (300 ml), perchloric acid 42 ml, 60% aqueous), and water (198 ml) and stirred at room temperature for 1½ hr. Isolation of the steroid using ether gave crude 3 $\beta$ -acetoxy-5 $\alpha$ ,6 $\beta$ -dihydroxyandrostan-17-one (5.5 gm). Acetylation of this steroid with acetic anhydride (5.5 ml) in pyridine (28 ml) at room temperature for 12 hr. gave, after chromatography on deactivated alumina (400 g), 3 $\beta$ ,6 $\beta$ -diacetoxy-5 $\alpha$ -hydroxyandrost-17-one (72a) (2.14 g) as needles from ethanol, m.p. 218-219°, [ $\alpha$ ]<sub>D</sub> -7° (c, 1.4), (Lit.cit.,<sup>95</sup> m.p. 212-214°,  $\nu$  max. 3504, 1742, 1723 cm<sup>-1</sup>. N.m.r.  $\delta$  5.12 (W<sub>2</sub><sup>h</sup> 20Hz; C(3)H), 4.63 (W<sub>2</sub><sup>h</sup> 5Hz; C(6)H), 2.08, 2.02 (C(3)OAc, C(6)OAc), 1.16 (C(19)H<sub>3</sub>), 0.88 (C(18)H<sub>3</sub>) ppm. (Found: C, 67.8; H, 8.3. C<sub>23</sub>H<sub>34</sub>O<sub>6</sub> requires C, 68.0; H, 8.4%.

3 $\beta$ ,5 $\alpha$ ,6 $\beta$ -Triacetoxyandrostan-17-one

A solution of 3 $\beta$ ,6 $\beta$ -diacetoxy-5 $\alpha$ -hydroxyandrostan-17-one (72a) (1.0 g) in carbon tetrachloride (80 ml) and acetic anhydride (7 ml, containing 7 drops of 70% aqueous perchloric acid) was stirred at room temperature for 2 min. The steroidal material was isolated by means of ether and adsorbed onto deactivated alumina (12 g). Elution with ether gave 3 $\beta$ ,5 $\alpha$ ,6 $\beta$ -triacetoxyandrostan-17-one (72b) as stars from ethanol, m.p. 185-186° (Lit.cit.,<sup>64,72</sup> 184-185°), [ $\alpha$ ]<sub>D</sub> -3° (c, 1.7)

$\nu_{\max}$ . 1753, 1740  $\text{cm}^{-1}$ . N.m.r.  $\delta$  5.92 ( $\text{W}_{\frac{1}{2}}$  5Hz; C(6)H), 4.73 ( $\text{W}_{\frac{1}{2}}$  18Hz; C(3)H), 2.00 and 2.10 (C(3)OAc, C(6)OAc), 1.23 (C(19)H<sub>3</sub>), 0.90 (C(18)H<sub>3</sub>) ppm. (Found: C, 66.7; H, 7.9.  $\text{C}_{25}\text{H}_{36}\text{O}_7$  requires C, 66.9; H, 8.1%)

Reaction of 3 $\beta$ ,6 $\beta$ -diacetoxy-5 $\alpha$ -hydroxyandrost-17-one with



To a solution of 3 $\beta$ ,6 $\beta$ -diacetoxy-5 $\alpha$ -hydroxyandrost-17-one (72a) (500 mg) in acetic anhydride (5 ml) and acetic acid (20 ml) was added a solution of sulphuric acid (5 ml, 1% w/v) in acetic acid and the reaction mixture stirred at 45° for 7 min. The steroidal material was isolated by means of ether-benzene (1:1) and adsorbed onto deactivated alumina (30 gm). Elution with light petroleum-benzene (1:1) gave an inseparable mixture of 3 $\beta$ ,6 $\beta$ -diacetoxyandrost-4-en-17-one (75) and 3 $\beta$ ,6 $\beta$ -diacetoxy-5 $\beta$ -methyl-19-norandrost-9(10)-en-17-one (74) (1:4 by n.m.r.) (142 mg). Elution with benzene gave 3 $\beta$ ,6 $\beta$ -diacetoxy-5 $\beta$ -methyl-19-norandrost-9(10)-en-17-one (74 (132 mg) as needles from methanol,  $[\alpha]_D +143^\circ$  (c, 1.7, (Lit.cit.,<sup>64</sup>  $[\alpha]_D +158^\circ$ ),  $\nu_{\max}$ . 2951-2959, 2896, 2870, 1738-1748  $\text{cm}^{-1}$ . N.m.r.<sup>63</sup>  $\delta$  5.08 (t, J = 3Hz; C(3)H), 4.72, (q, J = 9Hz, J' = 6Hz; C(6)H) 2.06 (C(3)OAc, C(6)OAc), 1.25 (C(5 $\beta$ )CH<sub>3</sub>), 1.00 (C(18)H<sub>3</sub>) ppm. (Found: (M<sup>+</sup>-60) 328.203851.  $\text{C}_{23}\text{H}_{32}\text{O}_5$  requires M<sup>+</sup> 388, (M<sup>+</sup>-HOAc) 328.203833). Elution with benzene-ether (4:1) gave 3 $\beta$ ,5,6 $\beta$ -triacetoxy-5 $\alpha$ -androst-17-one (72b) (15 mg) identical to an authentic sample. Elution with ether gave unreacted 3 $\beta$ ,6 $\beta$ -diacetoxy-5-hydroxy-5 $\alpha$ -androst-17-one (72a) (20 mg), m.p. 218-219°,  $[\alpha]_D -7^\circ$ .

Reaction of  $3\beta,5,6\beta$ -triacetoxy- $5\alpha$ -androstan-17-one with  $\text{BF}_3 \cdot \text{Et}_2\text{O} \cdot \text{Ac}_2\text{O}$  <sup>67</sup>.

$\text{BF}_3 \cdot \text{Etherate}$  (1.5 ml) was added to a solution of  $3\beta,5,6\beta$ -triacetoxy- $5\alpha$ -androstan-17-one (72b) (733 mg) in acetic anhydride (75 ml) and the mixture stirred at  $85-90^\circ$  for 20 min. Isolation of the product mixture by means of ether-ethyl acetate (1:1) gave a dark brown organic tar which was chromatographed on deactivated alumina (25 g) three times to remove the highly polar tar (280 mg). Elution with light petroleum-benzene (7:3) gave an unidentified aromatic compound (18 mg), as a gum,  $\nu_{\text{max.}} 1735 \text{ cm}^{-1}$ . N.m.r. 7.32 - 7.90 (aromatic protons), 4.30 (t,  $J = 6\text{Hz}$ ), 0.93 ( $\text{C}(18)\text{H}_3$ ) ppm. An orange colour forms with tetranitromethane. Elution with benzene gave an inseparable mixture of  $3\beta,6\beta$ -diacetoxyandrost-4-en-17-one (75) and  $3\beta,6\beta$ -diacetoxy- $5\beta$ -methyl-19-norandrost-9(10)-en-17-one (74) (40 mg). Further elution with benzene gave  $3\beta,6\beta$ -diacetoxy- $5\beta$ -methyl-19-norandrost-9(10)-en-17-one (74) (30 mg) identical to an authentic sample. Elution with ether gave unreacted  $3\beta,5,6\beta$ -triacetoxy- $5\alpha$ -androstan-17-one (72b) (120 mg).

Reaction of  $3\beta,6\beta$ -diacetoxy-5-hydroxy- $5\alpha$ -androstan-17-one with thionyl chloride-pyridine.

A solution of  $3\beta,6\beta$ -diacetoxy-5-hydroxy- $5\alpha$ -androstan-17-one (72a) (100 mg) in dry pyridine (5 ml) was cooled to freezing in a dry ice - chloroform bath then thionyl chloride (0.4 ml) was added and the reaction mixture stirred and slowly warmed. As soon as a light red colour developed the steroid was isolated with ether to give  $3\beta,6\beta$ -diacetoxyandrost-4-en-17-one (75) as plates from methanol, m.p.  $151-154^\circ$ ,  $[\alpha]_D +44^\circ$  (c, 1.3), (Lit.cit., <sup>94</sup> m.p.  $163-164^\circ$ ,  $[\alpha]_D +56^\circ$ ),  $\nu_{\text{max.}} 1734$

$\text{cm}^{-1}$ . N.m.r.  $^{63}\text{S}$  5.65 ( $\text{W}_{\frac{1}{2}}^{\text{h}}$  4Hz; C(4)H), 5.33 (t,  $J = 3\text{Hz}$ ; C(3)H), 5.10 (q,  $J = 11\text{Hz}$ ,  $J' = 6\text{Hz}$ ; C(6)H), 2.05 (C(3)OAc, C(6)OAc), 1.20 (C(19) $\text{H}_3$ ), 0.93 (C(18) $\text{H}_3$ ) ppm.

### Pyrolysis of Vitamin D<sub>3</sub>.

Vitamin D<sub>3</sub> (88) (25 g) in decalin (21 ml) was heated under reflux conditions for 2 hr. The solution was cooled, diluted with benzene and adsorbed onto 5% deactivated alumina (1 kg). Elution with benzene in the dark with nitrogen being passed continually through the eluting solvent gave 10 $\alpha$ -cholesta-5,7-dien-3 $\beta$ -ol (83b) (14.77 g) contaminated with decalin. Further elution with benzene gave 9 $\beta$ -cholesta-5,7-dien-3 $\beta$ -ol (85b) (9.16 g) as a gum,  $[\alpha]_{\text{D}} +184^{\circ}$  (c, 1.03),  $\nu_{\text{max.}}$  3331  $\text{cm}^{-1}$ . N.m.r. 5.63 (d,  $J = 6\text{Hz}$ ; C(7)H, 5.24, 5.29, 5.34, 5.38, 5.43, 5.49, (C(6)H), 3.47, ( $\text{W}_{\frac{1}{2}}^{\text{h}}$  20Hz; C(3)H), 1.24 (C(19) $\text{H}_3$ ), 0.64 (C(18) $\text{H}_3$ ) ppm. The gum containing decalin was diluted with light petroleum and adsorbed onto 5% deactivated alumina (200 g). Elution with benzene gave 10 $\alpha$ -cholesta-5,7-dien-3 $\beta$ -ol (83b) (9.3 g) as needles from light petroleum, m.p. 78-80 $^{\circ}$ ,  $[\alpha]_{\text{D}} +244^{\circ}$  (c, 1.15),  $\nu_{\text{max.}}$  3328  $\text{cm}^{-1}$ . N.m.r.  $\delta$  5.23, 5.33, 5.47, 5.57 (C(6)H, C(7)H), 4.02 ( $\text{W}_{\frac{1}{2}}^{\text{h}}$  7Hz; C(3)H), 1.98 (disappears on shaking with D<sub>2</sub>O; OH), 1.09 (C(19) $\text{H}_3$ ), 0.56 (C(18) $\text{H}_3$ ) ppm.

### 9 $\beta$ -Cholesta-4,7-dien-3-one

A solution of 9 $\beta$ -cholesta-5,7-dien-3 $\beta$ -ol (85b) (10.1 g) in toluene (225 ml) and cyclohexanone (45 ml) was dried by azeotropic distillation in the dark. Aluminium isopropoxide (6.7 g) dissolved in dry

distillate (50 ml) was added and the mixture refluxed in the dark for 5 hr. The steroid was isolated by pouring the mixture onto HCl (1M; 500 ml) and ice, followed by extraction with ether. The crude steroid, contaminated with cyclohexanone polymers was adsorbed onto 5% deactivated alumina (1 kg) and eluted with light petroleum until no more non-steroidal material was obtained. Elution with benzene gave 9 $\beta$ -cholesta-4,7-dien-3-one (89b) (8.08 g) as small needles from methanol, m.p. 110-111.5 $^{\circ}$ ,  $\nu_{\text{max}}$ . 1674, 1628  $\text{cm}^{-1}$ ,  $\lambda_{\text{max}}$ . 244 nm, ( $\epsilon$  13,200), yellow colour with tetranitromethane. N.m.r.  $\delta$  5.68 ( $\text{W}_{\frac{h}{2}}$  2.5Hz; C(4)H), 5.52 ( $\text{W}_{\frac{h}{2}}$  11Hz; C(7)H), 1.23 (C(19)H $_3$ ), 0.57 (C(18)H $_3$ ) ppm.

#### 9 $\beta$ -cholesta-4,6-dien-3-one

A solution of 9 $\beta$ -cholesta-4,7-dien-3-one (89b) (2.1 g) in dry chloroform (175 ml) was stirred with a solution of hydrogen bromide (45% w/v in acetic acid; 2.5 ml) at room temperature for 40 min. Pyridine was added until only a light yellow colour remained and the solvent evaporated. The residue was dissolved in light petroleum, filtered, and adsorbed onto deactivated alumina (100 g). Elution with light petroleum-benzene (4:1) gave 9 $\beta$ -cholesta-4,8(14)-dien-3-one (91) (1.14 g) as a powder from acetone-methanol, m.p. 76-78 $^{\circ}$ ,  $\nu_{\text{max}}$ . 1725  $\text{cm}^{-1}$ ,  $\lambda_{\text{max}}$ . 241 nm, ( $\epsilon$  15,700), 248.5 nm, ( $\epsilon$  10,900), red colour with tetranitromethane. N.m.r.  $\delta$  5.40 ( $\text{W}_{\frac{h}{2}}$  6Hz; C(4)H), 1.25 (C(19)H $_3$ ), 0.85 (C(18)H $_3$ ) ppm. (Found:  $M^+$  382.323549. Expected for C $_{27}$ H $_{42}$ O:  $M^+$  382.323549). Elution with light petroleum-benzene (1:1) gave 9 $\beta$ -cholesta-4,6-dien-3-one (92) (400 mg) as a gum,  $\nu_{\text{max}}$ . 1668, 1623, 1588  $\text{cm}^{-1}$ ,  $\lambda_{\text{max}}$ . 285.5 nm, ( $\epsilon$  1,800), yellow colour with



tetranitromethane. N.m.r.  $\delta$  6.05 ( $W_{\frac{h}{2}}$  5Hz; C(6)H, C(7)H), 5.72 (C(4)H), 1.26 (C(19)H<sub>3</sub>), 0.90 (C(18)H<sub>3</sub>) ppm.

5 $\xi$ ,9 $\beta$ -cholest-8(14)-en-3-one

A solution of 9 $\beta$ -cholesta-4,8(14)-dien-3-one (91) (116 mg) in ethanol (4 ml) and a solution of potassium hydroxide (6.1 ml; 0.87 mg/ml) in ethanol were shaken with 5% palladium on charcoal (18 mg) under hydrogen (1520 psi) at room temperature for 2 hr. A few drops of pyridine and acetic acid were added, the mixture filtered, and the solvent evaporated under reduced pressure. The steroidal material was isolated using ether giving 5 $\xi$ ,9 $\beta$ -cholest-8(14)-en-3-one (93) (97 mg) as a gum,  $\nu_{\text{max}}$ . 1716 cm<sup>-1</sup>,  $\lambda_{\text{max}}$ . 200 nm, ( $\epsilon$  7,000), orange colour with tetranitromethane. N.m.r.  $\delta$  0.90 (C(19)H<sub>3</sub>, C(18)H<sub>3</sub>) ppm.

5 $\xi$ ,9 $\beta$ -Cholest-7-en-3-one

A solution of 9 $\beta$ -cholesta-4,7-dien-3-one (89b) (101 mg) in ethanol and a solution of potassium hydroxide (6.1 ml; 0.87 mg/ml) in ethanol were shaken with 5% palladium on charcoal (20 mg) under hydrogen (1400 psi) for 2 hr. Isolation of the steroid in the usual way gave 5 $\xi$ ,9 $\beta$ -cholest-7-en-3-one (94) (100 mg) as a gum,  $\nu_{\text{max}}$ . 1716 cm<sup>-1</sup>,  $\lambda_{\text{max}}$ . 200 nm ( $\epsilon$  5,000). N.m.r.  $\delta$  5.17 ( $W_{\frac{h}{2}}$  9Hz; C(7)H), 1.27 (C(19)H<sub>3</sub>), 0.78 (C(18)H<sub>3</sub>) ppm.

Attempted Oppenauer oxidation of 10 $\alpha$ -cholesta-5,7-dien-3-ol.

A solution of 10 $\alpha$ -cholesta-5,7-dien-3 $\beta$ -ol (83b) (15 g) in toluene (400 ml) and cyclohexanone (55 ml) was dried by azeotropic distillation in the dark. Aluminium isopropoxide (10 gm) dissolved in dry distillate (50 ml) was added and the mixture refluxed under nitrogen in the dark

for 4 hr. The mixture was poured into HCl (1M) and ice (500 ml) and the organic phase separated and washed. Evaporation of the solvent and steam distillation gave an inseparable mixture of 10 $\alpha$ -cholesta-4,7-dien-3-one (90b) and cyclohexanone polymers,  $\nu_{\text{max}}$ . 1670, 1630  $\text{cm}^{-1}$ . N.m.r.  $\delta$  5.85 ( $W_{\frac{h}{2}}$  4Hz; C(4)H), 5.01 ( $W_{\frac{h}{2}}$  9Hz; C(7)H), 1.25 (C(19)H<sub>3</sub>), 0.65 (C(18)H<sub>3</sub>) ppm.

10 $\alpha$ -cholesta-5,7-dienyl-3 $\beta$ -benzoate.

A solution of 10 $\alpha$ -cholesta-5,7-dien-3 $\beta$ -ol (83b) (499 mg) in dry pyridine (25 ml) and benzoyl chloride (0.48 ml) was stirred at 4° for 20 hr. The steroidal material was isolated using ether and adsorbed onto 5% deactivated alumina (50 g). Elution with light petroleum gave 10 $\alpha$ -cholesta-5,7-dienyl-3 $\beta$ -benzoate (83d) (500 mg) as an oil,  $[\alpha]_D^{25} +141^\circ$  (c, 1.1),  $\nu_{\text{max}}$ . 1724, 720  $\text{cm}^{-1}$ ,  $\lambda_{\text{max}}$ . 214 nm, ( $\epsilon$  9,100), 273.5 nm, ( $\epsilon$  2,600), 283 nm ( $\epsilon$  2,300), 295 nm, ( $\epsilon$  1,400). N.m.r.  $\delta$  7.35-8.08 (C(3 $\beta$ )-benzoate), 5.38 ( $W_{\frac{h}{2}}$  18Hz; C(3)H, C(6)H, C(7)H), 1.11 (C(19)H<sub>3</sub>), 0.56 (C(18)H<sub>3</sub>) ppm.

10 $\alpha$ -Cholesta-5,7-dienyl-3 $\beta$ -acetate

A solution of 10 $\alpha$ -cholesta-5,7-dien-3 $\beta$ -ol (83b) (2.2 g) in pyridine (25 ml) and acetic anhydride (6 ml) was stirred at room temperature under nitrogen in the dark overnight. Isolation of the steroid using ether and chromatography on 5% deactivated alumina (150 g) gave 10 $\alpha$ -cholesta-5,7-dienyl-3 $\beta$ -acetate (83c) as needles from pentane, identical to an authentic sample, <sup>96</sup> m.p. 121-122°,  $\nu_{\text{max}}$ . 1735  $\text{cm}^{-1}$ . N.m.r.  $\delta$  5.35 (d,  $J$  = 6Hz; C(6)H), 5.60 (d,  $J$  = 6Hz, C(7)H), 4.95 ( $W_{\frac{h}{2}}$  7Hz; C(3)H), 1.97 (OAc), 1.05 (C(19)H<sub>3</sub>), 0.56 (C(18)H<sub>3</sub>) ppm.

9 $\beta$ -Cholest 5,7-dienyl-3 $\beta$ -acetate

A solution of 9 $\beta$ -cholest 5,7-dien-3 $\beta$ -ol (85b) (2.2 g) in pyridine (25 ml) and acetic anhydride (6 ml) was stirred at room temperature under nitrogen in the dark overnight. Isolation of the steroid using ether and chromatography on 5% deactive alumina gave 9 $\beta$ -cholesta-5,7-dienyl-3 $\beta$ -acetate (85c) (2 g) as a gum,  $\nu_{\text{max}}$  1738  $\text{cm}^{-1}$ . N.m.r.  $\delta$  5.67 (d,  $J = 6\text{Hz}$ ; C(6)H), 5.40 (d,  $J = 6\text{Hz}$ ; C(7)H), 5.32 ( $\text{W}_{\frac{1}{2}}^{\text{H}}$  9Hz; C(3)H), 1.95 (OAc), 1.18 (C(19)H<sub>3</sub>), 0.63 (C(18)H<sub>3</sub>) ppm.

REACTIONS OF STEROIDAL DIENES WITH DIENOPHILES

Reactions of steroidal  $\Delta^{5,7}$ -dienes with alkenes have, in addition to giving  $[\pi 4 + \pi 2]$  adducts, resulted in the formation of a number of interesting and unexpected products. Cholest $\alpha$ -5,7-dienyl-3 $\beta$ -benzoate (97) and ergosteryl acetate (98) react with tetracyanoethylene (TCNE) to give 7 $\alpha$ -(1,1,2,2-tetracyanoethyl)-cholest $\alpha$ -5,8(14)-dienyl-3 $\beta$ -benzoate (99)<sup>74</sup> and 7 $\alpha$ -(1,1,2,2-tetracyanoethyl)-ergost $\alpha$ -5,8(14),22-trienyl-3 $\beta$ -acetate (100)<sup>75</sup> respectively. These are examples of an "ene" reaction (Figure 6)<sup>74</sup>.

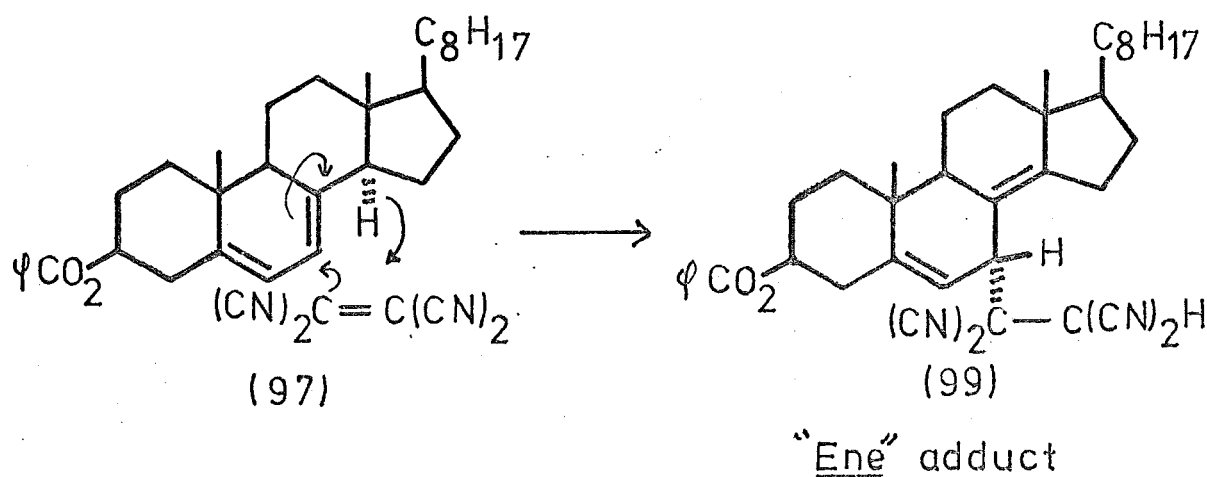


Figure 6

9(11)-Dehydroergosteryl acetate (101) on reaction with TCNE gave both the "ene" product, 7 $\alpha$ -(1,1,2,2-tetracyanoethyl)-ergost $\alpha$ -5,8(14),9(11),22-tetraenyl-3 $\beta$ -acetate (102) (29%) and 7 $\alpha$ ,15 $\alpha$ -tetracyan-

oethyl-ergost-5,8(14),9(11),22-tetraenyl-3 $\beta$ -acetate (103) (25%).

This latter product is thought to arise from reaction of TCNE with ergosta-5,7,9(11),14(15),22-pentaenyl-3 $\beta$ -acetate (104), an intermediate formed by elimination from adduct (102). In contrast 10 $\alpha$ ,9 $\beta$ -luminosteryl acetate (105) failed to react with TCNE <sup>74</sup>. The inability of natural steroidal  $\Delta^{5,7}$ -dienes to form [ $\pi 4 + \pi 2$ ] adducts with TCNE probably results from the steric interference between the approaching TCNE and the 10 $\beta$ - and 13 $\beta$ - methyls on the  $\beta$ -face and with the 9 $\alpha$ -, 1 $\alpha$ -, and 12 $\alpha$ - protons on the  $\alpha$ -face <sup>76</sup>. The failure of lumisteryl acetate (105) to react with TCNE can similarly be accounted for by steric interference to the approaching dienophile <sup>77</sup>.

Steroidal cisoid-dienes in less hindered environments readily form [ $\pi 4 + \pi 2$ ] adducts. 3 $\beta$ -Acetoxyergosta-6,8(14),9(11),22-tetraene (106) reacts with TCNE to give the ring C 11 $\alpha$ ,14 $\alpha$ -cycloadduct (107) <sup>76</sup>. Ergosta-7,14,22-trienyl-3 $\beta$ -benzoate (108) on reaction with TCNE gives a 7 $\alpha$ ,15 $\alpha$ -cycloadduct (109) <sup>76</sup>.

Dienophiles, such as maleic anhydride and 4-phenyl-1,2,4-triazoline-3,5-dione (110)<sup>80</sup> which, in contrast to TCNE, have one side free of bulky substituents are able to form cycloadducts with ring B dienes <sup>85</sup>.

For example, luminosteryl acetate (105) on reaction with maleic anhydride gives the 5 $\alpha$ ,8 $\alpha$ -cycloadduct (111) <sup>74</sup>.

In this study, we have investigated the reaction of 3 $\beta$ -substituted 10 $\alpha$ -cholesta-5,7-dienes and 9 $\beta$ -cholesta-5,7-dienes with tetracyanoethylene, 4-phenyl-1,2,4-triazoline-3,5-dione, and maleic anhydride. The latter reagent was found unsuitable as the higher temperatures required for reaction led to decomposition of the steroidal dienes.

9 $\beta$ -Cholesta-5,7-dien-3 $\beta$ -ol (85b) reacted with TCNE in dichloromethane

to give 7 $\alpha$ -(1,1,2,2-tetracyanoethyl)-9 $\beta$ -cholesta-5,8(14)-dien-3 $\beta$ -ol (112) in high yield. The n.m.r. spectrum showed the C(6)-olefin proton as a doublet ( $J = 6\text{Hz}$ ) centred at  $\delta$  5.35 and the C(7)-proton as a doublet ( $J = 6\text{Hz}$ ) centred at  $\delta$  3.56. The coupling of the C(6)H and C(7)H was confirmed by double irradiation experiments. The active  $-\underline{\text{CH}}(\text{CN})_2$  proton of the adduct was a singlet centred at  $\delta$  4.35. This proton underwent rapid exchange with  $\text{D}_2\text{O}$ . The  $\Delta^{8(14)}$ -double bond was demonstrated by the characteristic<sup>78</sup> deshielding of C(18) $\text{H}_3$  and the slight shielding of C(19) $\text{H}_3$  causing both peaks to occur at  $\delta$  0.97. For abstraction of the 14 $\alpha$ -proton, reaction with TCNE must have occurred on the undersurface of the steroid leading to the 7 $\alpha$ -configuration of the adduct (Figure 7).

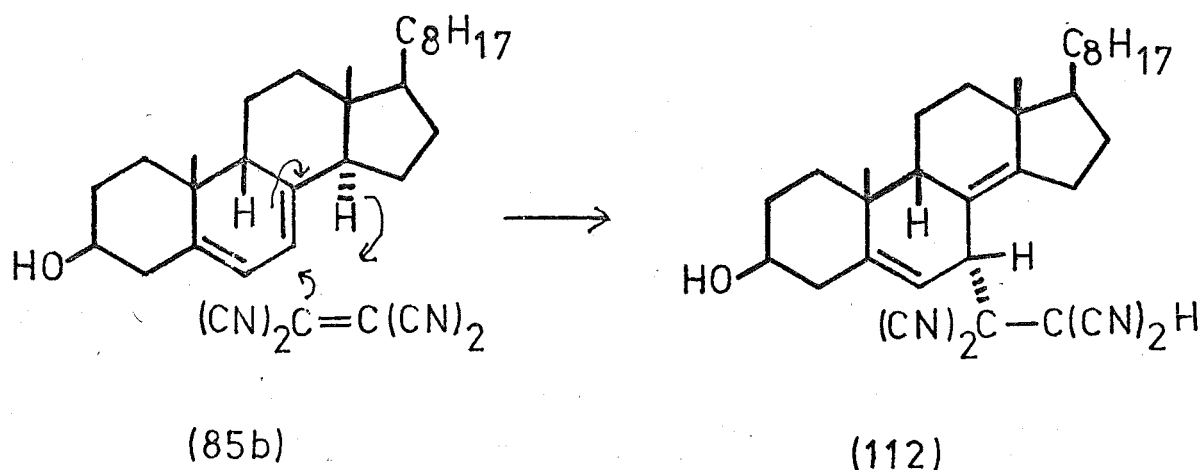


Figure 7

An alternative product,  $7\beta$ -(1,1,2,2-tetracyanoethyl)- $9\beta$ -cholesta-5,8(9)-dien- $3\beta$ -ol (113) can be excluded as the  $\Delta^{8(9)}$ -double bond would deshield  $C(19)H_3$  and give a separation of ca 34Hz between the  $C(19)H_3$  and  $C(18)H_3$  peaks in the n.m.r. spectrum. Abstraction of the  $9\beta$ -proton by TCNE to form this compound is not favoured as a large interaction with the  $13\beta$ -methyl group would occur in the transition state.

Isolation of the products from reaction of TCNE with  $10\alpha$ -cholesta-5,7-dien- $3\beta$ -ol (83b) proved difficult. Reaction of TCNE with  $10\alpha$ -cholesta-5,7-dienyl- $3\beta$ -benzoate (83d) however gave  $5\alpha,8\alpha$ -tetracyanoethyl- $10\alpha$ -cholest-6-enyl- $3\beta$ -benzoate (114b) (50%) which crystallized out of the product mixture, and  $7\alpha$ -(1,1,2,2-tetracyanoethyl)- $10\alpha$ -cholesta-5,8(14)-dienyl- $3\beta$ -benzoate (115b) (50%). This latter product could not be obtained pure as it was unstable. The n.m.r. spectrum of the  $5\alpha,8\alpha$ -cycloadduct (114b) showed the C(6) and C(7) olefinic protons as an AB quartet ( $\delta_A$  6.98,  $\delta_B$  6.42,  $J_{AB}$  = 10Hz). The C(10)-methyl was deshielded to  $\delta$  1.57 by nitrile groups (Figure 8). The mass spectrum showed a weak parent ion at  $m/e$  616 corresponding to a molecular formula  $C_{40}H_{48}N_4O_2$ .

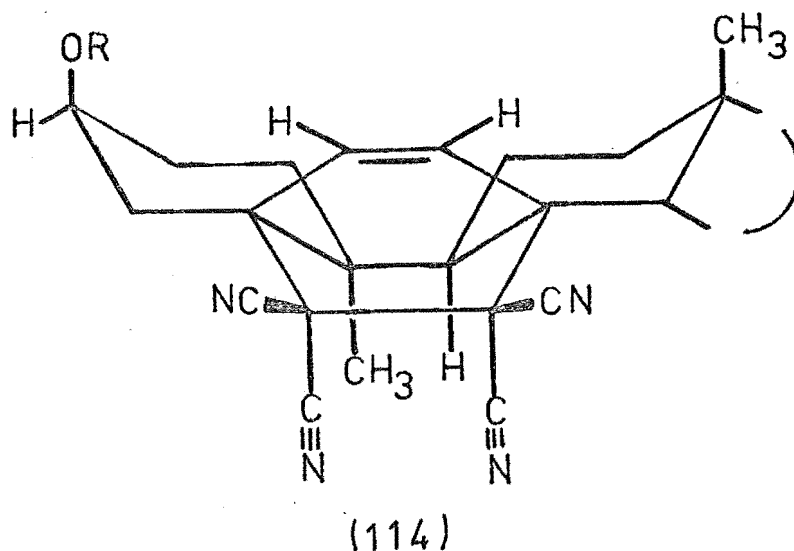


Figure 8

Addition of the TCNE to 10 $\alpha$ -cholesta-5,7-dienyl-3 $\beta$ -benzoate (83d) occurs from the  $\alpha$ -face. Approach from the  $\beta$ -face is hindered by the 13 $\beta$ -methyl group. Dreiding models demonstrate that the alternative 5 $\beta$ ,8 $\beta$ -cyclo adduct could not exist since a nitrile group and the 13 $\beta$ -methyl would be coincident.

The ene adduct (115b) was assigned on the basis of its n.m.r. spectrum. The C(6) and C(7) protons are doublets ( $J = 4.5\text{Hz}$ ) centred at  $\delta$  5.37 and  $\delta$  3.62 respectively and were shown to be coupled to each other by double irradiation experiments. The active  $-\underline{\text{CH}}(\text{CN})_2$  proton centred at  $\delta$  4.48 was identified by exchange on shaking with  $\text{D}_2\text{O}$ . The 8(14)-position of the double bond follows from the deshielding<sup>78</sup> of  $\text{C}(18)\text{H}_3$  and the slight shielding of  $\text{C}(19)\text{H}_3$ . Both the  $\text{C}(18)\text{H}_3$  and the  $\text{C}(19)\text{H}_3$  were centred at  $\delta$  0.89.

9 $\beta$ -Cholesta-5,7-dienyl-3 $\beta$ -acetate (85c) reacted with 4-phenyl-1,2,4-triazoline-3,5-dione (110) to give the 3 $\beta$ -acetoxy-9 $\beta$ -cholest-6-ene-5 $\alpha$ ,8 $\alpha$ -cycloadduct (116) in 77% yield. The structure of the adduct follows from the n.m.r. spectrum. The C(6) and C(7) olefinic protons gave an AB quartet ( $\delta_{\text{A}} 6.50$ ,  $\delta_{\text{B}} 6.15$ ,  $J_{\text{AB}} = 8\text{Hz}$ ), and the phenyl group was a multiplet centred at  $\delta$  7.40. The molecular ion was found in the 70eV mass spectrum at 601 (4%) corresponding to a molecular formula,  $\text{C}_{37}\text{H}_{51}\text{O}_4\text{N}_3$ . Two intense peaks occurred at 424 (65%) (corresponding to  $\text{C}_{29}\text{H}_{44}\text{O}_2$ ) and 177 (60%) (corresponding to  $\text{C}_8\text{H}_7\text{N}_3\text{O}_2$ ) and these are thought<sup>79</sup> to arise by a double McLafferty fragmentation as shown in Figure 9. Similar spectral information has been obtained from the 5 $\alpha$ ,8 $\alpha$ -cycloadduct formed from 4-phenyl-1,2,4-triazoline-3,5-dione and 3 $\beta$ -acetoxyergosta-5,7-diene<sup>80</sup>.



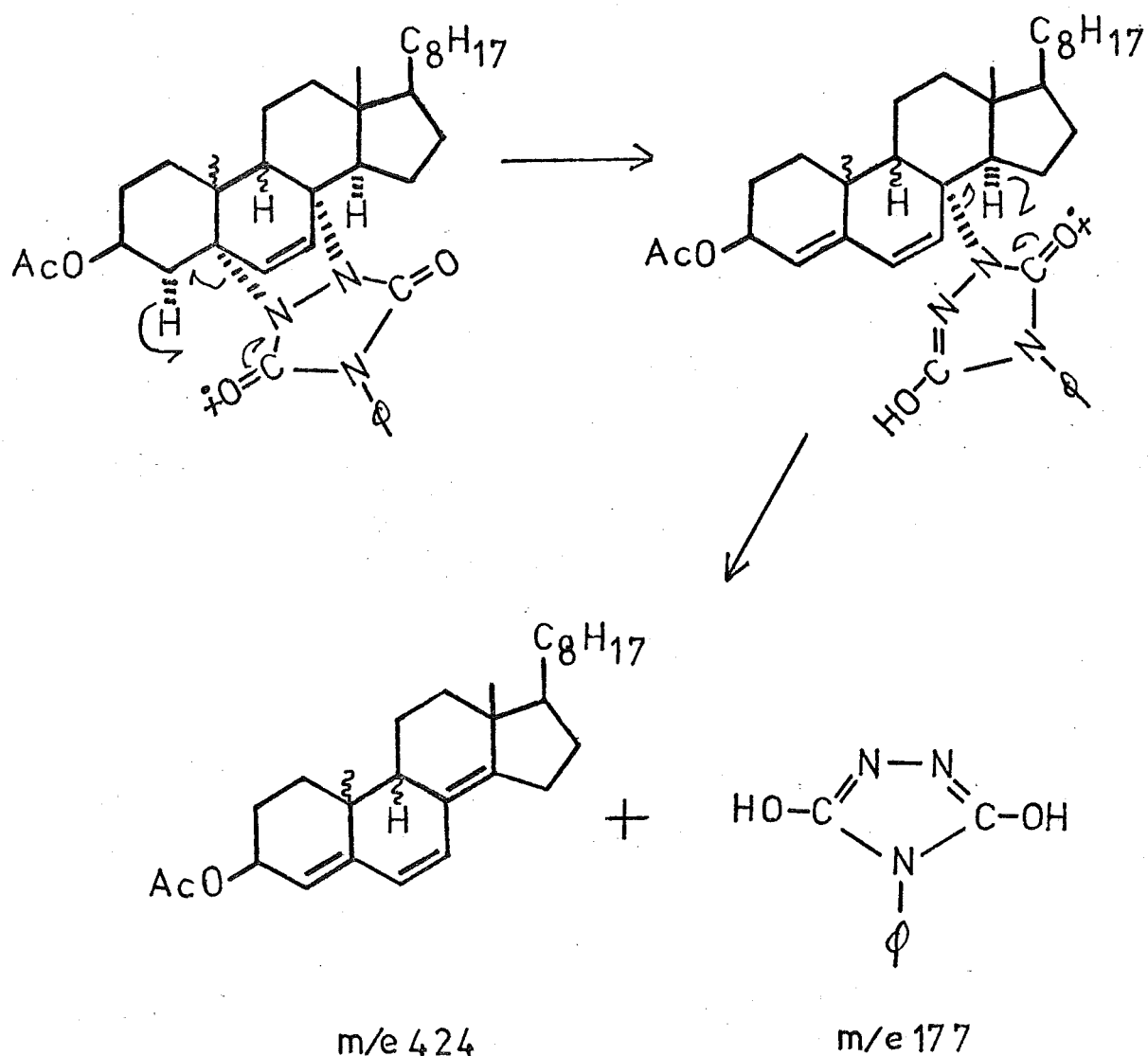


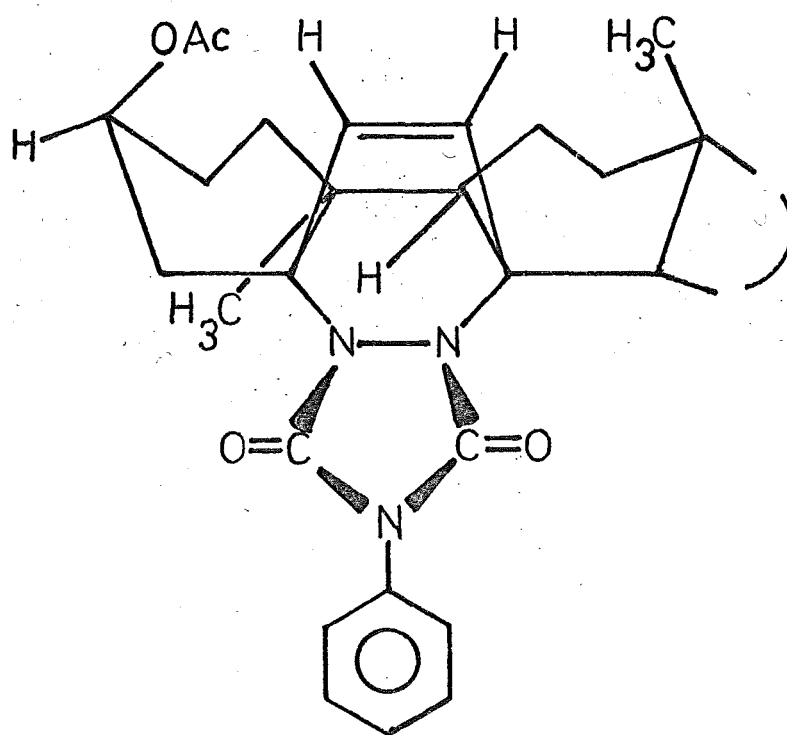
Figure 9

3 $\beta$ -Acetoxy-10 $\alpha$ -cholesta-5,7-diene (83c) reacted with 4-phenyl-1,2,4-triazoline-3,5-dione (110) to give the 3 $\beta$ -acetoxy-10 $\alpha$ -cholest-6-ene-5 $\alpha$ ,8 $\alpha$ -cycloadduct (117) in 95% yield. The n.m.r. spectrum was similar to the 9 $\beta$ -analogue with the C(6) and C(7) protons forming an AB pattern ( $\delta_A$  6.75,  $\delta_B$  6.42,  $J_{AB}$  = 8Hz). No molecular ion was found in the 70eV mass spectrum. The intense peaks caused by

a double McLafferty fragmentation (Figure 9) were however found at 424 ( $C_{29}H_{44}O_2$ ) and 177 ( $C_8H_7N_3O_2$ )<sup>80</sup>.

The  $13\beta$ -methyl group appears to dominate the chemistry of additions to  $\Delta^{5,7}$ -dienes. In each of the  $9\alpha,10\alpha$ -,  $9\beta,10\beta$ -,  $9\alpha,10\beta$ -, and  $9\beta,10\alpha$ -  $\Delta^{5,7}$ -dienes the  $13\beta$ -methyl group hinders access to C(8) from the upper surface of the molecule. Approach to C(8) and C(5) from the under surface is also hindered. The  $\alpha$ -face is hindered for the  $9\alpha,10\beta$ - $\Delta^{5,7}$ -diene (98) by the  $1\alpha$ -,  $9\alpha$ -, and  $12\alpha$ -hydrogens; the  $9\beta,10\alpha$ - $\Delta^{5,7}$ -diene (105) by the  $2\alpha$ -,  $11\alpha$ -,  $14\alpha$ -hydrogens, and the  $10\alpha$ -methyl; and the  $9\beta,10\beta$ - $\Delta^{5,7}$ -diene (85) by the  $1\alpha$ -,  $12\alpha$ -, and  $14\alpha$ -hydrogens. In a molecule of the  $9\alpha,10\alpha$ - $\Delta^{5,7}$ -diene (83) the hydrogens ( $9\alpha$ -,  $12\alpha$ -, and  $14\alpha$ -) and the  $10\alpha$ -methyl that could cause steric hinderance are orientated away from C(5) and C(8) and allow access from underneath (Figure 10).

4-Phenyl-1,2,4-triazoline-3,5-dione (110) has bulky substituents only on one side of the molecule. Interactions with protons on the  $\alpha$ -face of the steroid are less important than with TCNE as the triazoline can orient itself such that the bulky side is away from the axial  $\alpha$ -protons which could cause steric hinderance (the  $1\alpha$ -,  $3\alpha$ -,  $11\alpha$ -,  $12\alpha$ -, and  $14\alpha$ -). It is therefore not surprising that cycloadduction of  $\Delta^{5,7}$ -dienes with triazoline occurs to give the products in Figures 10, 11.



(117)

Figure 10

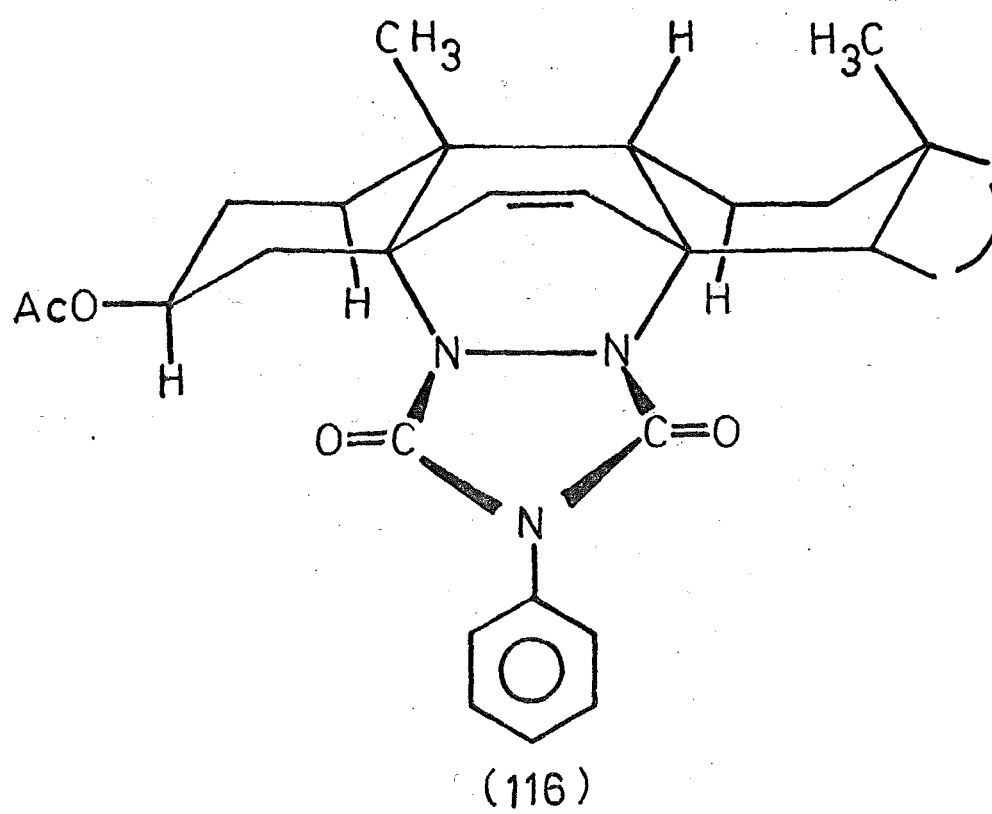


Figure 11

EXPERIMENTALTCNE adduct of  $9\beta$ -cholesta-5,7-dien- $3\beta$ -ol

To a solution of  $9\beta$ -cholesta-5,7-dien- $3\beta$ -ol (85b) (549 mg) in dichloromethane was added tetracyanoethylene (TCNE) (132 mg) and the mixture stirred at room temperature under nitrogen in the dark for 20 hr. Evaporation of the solvent gave  $7\alpha$ -(1,1,2,2-tetracyanoethyl)- $9\beta$ -cholesta-5,8(14)-dien- $3\beta$ -ol (112) (310 mg) as an off-white powder from light petroleum-methylene chloride, m.p. 157-159°,  $[\alpha]_D^{+254}$  (c, 0.98),  $\nu_{\max}$ . 3565, 2571, 1667  $\text{cm}^{-1}$ ,  $\lambda_{\max}$ . 202.5 nm, ( $\epsilon$  4,930).

N.m.r.  $\delta$  5.35 (d,  $J$  = 6Hz; collapses to a singlet on double irradiation at 3.56 ppm; C(6)H), 4.35 (disappears on shaking with  $\text{D}_2\text{O}$ ; C(2')H), 3.56 (d,  $J$  = 6Hz; collapses to a singlet on double irradiation at 5.35 ppm; C(7)H), 3.50 ( $W_{\frac{h}{2}}$  26Hz; C(3)H), 1.6 (disappears on shaking with  $\text{D}_2\text{O}$ ; OH), 0.97 (C(19) $\text{H}_3$ , C(18) $\text{H}_3$ ) ppm. (Found: ( $M^+$ -27) 485.  $\text{C}_{33}\text{H}_{44}\text{N}_4\text{O}$  requires:  $M^+$  512, ( $M^+$ -HCN) 485) (Found: C, 77.1; H, 8.8; N, 11.4.  $\text{C}_{33}\text{H}_{44}\text{N}_4\text{O}$  requires: C, 77.3; H, 8.7; N, 10.9%).

TCNE adducts of  $10\alpha$ -cholesta-5,7-dien- $3\beta$ -ol

TCNE (300 mg) was added to a solution of  $10\alpha$ -cholesta-5,7-dien- $3\beta$ -ol (83b) (1.004 g) in dichloromethane (50 ml) and the mixture stirred at room temperature under nitrogen in the dark for 20 hr. Evaporation of the solvent gave a red solid mixture of  $5\alpha,8\alpha$ -tetracyanoethyl- $10\alpha$ -cholest-6-en- $3\beta$ -ol (114a) (70% by n.m.r.);  $\delta$  7.10, 6.95, 6.37 (AB pattern,  $\delta_A$  7.02,  $\delta_B$  6.45,  $J_{AB}$  = 9Hz; C(6)H, C(7)H, 4.38 ( $W_{\frac{h}{2}}$  8Hz; C(3)H, 1.7 (OH), 1.47 (C(19) $\text{H}_3$ ), 0.82 (C(18) $\text{H}_3$ ) ppm; and

7 $\alpha$ -(1,1,2,2-tetracyanoethyl)-10 $\alpha$ -cholesta-5,8(14)-dien-3 $\beta$ -ol (115a) (30% by n.m.r.);  $\delta$  5.42 (d, J = 5Hz; C(6)H, 4.42 (disappears on shaking with D<sub>2</sub>O; C(2')H, 4.12 ( $W_{\frac{h}{2}}$  7Hz; C(3)H, 3.50 (d, J = 5Hz; C(7)H ppm. Attempted crystallization from light petroleum gave mainly tetracyanoethane and a very small quantity of the  $[ \pi^4 + \pi^2 ]$  cycloadduct (114a). Chromatography on silica gave, on elution with light petroleum-benzene (1:1) a mixture of the adducts, and elution with benzene gave a very small quantity of the  $[ \pi^4 + \pi^2 ]$  cycloadduct.

#### TCNE adducts of 10 $\alpha$ -cholesta-5,7-dienyl-3 $\beta$ -benzoate

TCNE (94 mg) was added to a solution of 10 $\alpha$ -cholesta-5,7-dienyl-3 $\beta$ -benzoate (83d) (419 mg) in dichloromethane (50 ml) and the mixture stirred at room temperature under nitrogen in the dark for 20 hr. Evaporation of the solvent gave a 1:1 mixture (by n.m.r.) of 5 $\alpha$ ,8 $\alpha$ -tetracyanoethyl-10 $\alpha$ -cholest-6-enyl-3 $\beta$ -benzoate (114b) and 7 $\alpha$ -(1,1,2,2-tetracyanoethyl)-10 $\alpha$ -cholesta-5,8(14)-dienyl-3 $\beta$ -benzoate (115b). Crystallization from methanol gave the  $[ \pi^4 + \pi^2 ]$  cycloadduct (114b) as a powder (85 mg), m.p. 122-124°,  $[\alpha]_D^{+42}$  (c, 1.16),  $\nu_{\max}$ . 2250, 1725, 715 cm<sup>-1</sup>,  $\lambda_{\max}$ . 231 nm ( $\epsilon$  10,300), 273 nm ( $\epsilon$  820),  $[ \Phi ]_{221} + 9460$ ,  $[ \Phi ]_{228} - 2960$ ,  $[ \Phi ]_{242} + 6500$ ,  $\Delta\epsilon_{220} - 4.7$ ,  $\Delta\epsilon_{236} + 0.23$ . N.m.r.  $\delta$  7.38-8.13 (C(3 $\beta$ )-benzoate), 6.98, 6.83, 6.67, 6.52 (AB pattern,  $\delta_A$  6.98,  $\delta_B$  6.42,  $J_{AB} = 10$ Hz; C(6)H, C(7)H, 5.60 ( $W_{\frac{h}{2}}$  9Hz; C(3)H, 1.57 (C(19)H<sub>3</sub>), 0.87 (C(18)H<sub>3</sub>) ppm. (Found:  $M^+$  616, ( $M^+ - 27$ ) 589. C<sub>40</sub>H<sub>48</sub>N<sub>4</sub>O<sub>2</sub> requires:  $M^+$  616, ( $M^+ - \text{HCN}$ ) 589.) The ene adduct (115b) could not be obtained pure. N.m.r.  $\delta$  7.38 - 8.13 (C(3 $\beta$ )-benzoate), 5.62 ( $W_{\frac{h}{2}}$  9Hz; C(3)H, 5.37 (d, J = 4Hz; collapses to a singlet on double

irradiation at 3.62 ppm; C(6)H, 4.48 (C(2')H), 3.62, (d,  $J = 5\text{Hz}$ ;  
collapses to a singlet on double irradiation at 5.37 ppm; C(7)H,  
0.90 (C(18)H<sub>3</sub>, C(19)H<sub>3</sub>) ppm.

4-Phenyl-1,2,4-triazoline-3,5-dione adduct with 9 $\beta$ -cholesta-5,7-  
dienyl-3 $\beta$ -acetate.

To a solution of 9 $\beta$ -cholesta-5,7-dienyl-3 $\beta$ -acetate (85c) (500 mg) in dichloromethane (25 ml) was added a 4-phenyl-1,2,4-triazoline-3,5-dione (110) (206 mg) in dichloromethane (25 ml) and the mixture stirred at room temperature under nitrogen in the dark overnight. The steroidal material, left after the evaporation of solvent was dissolved in ether and filtered to remove solid material. Adding pentane gave the 3 $\beta$ -acetoxy-9 $\beta$ -cholest-6-ene-5 $\alpha$ ,8 $\alpha$ -cycloadduct (116) (542 mg) as small needles, m.p. 62-65°,  $[\alpha]_D^{25}(\text{MeOH}) +18$  (c, 1.09),  $\lambda_{\text{max}}$  250 nm ( $\epsilon$  4,000),  $\nu_{\text{max}}$  1744, 1696, 1605, 1507  $\text{cm}^{-1}$ . N.m.r.  $\delta$  7.40 ( $\text{W}_{\frac{h}{2}}$  11Hz; C(4')-phenyl), 6.55, 6.42, 6.18, 6.05 (AB pattern,  $\nu_A$  6.50  $\delta_B$  6.15,  $J_{AB} = 8\text{Hz}$ ; C(7)H, 5.55 ( $\text{W}_{\frac{h}{2}}$  9Hz; C(3)H, 1.97 (OAc), 1.13 (C(19)H<sub>3</sub>), 0.88 (C(18)H<sub>3</sub>) ppm. m/e 601, 426, 424, 366, 364 (100%), 177. (Found:  $M^+$  601.3882.  $\text{C}_{37}\text{H}_{51}\text{O}_4\text{N}_3$  requires  $M^+$  601.3878.) (Found: C, 72.6; H, 8.5; N, 6.7.  $\text{C}_{37}\text{H}_{51}\text{N}_3\text{O}_4$  requires: C, 73.8; H, 8.5; N, 7.0%.)

4-Phenyl-1,2,4-triazoline-3,5-dione adduct with 10 $\alpha$ -cholesta-5,7-dien-  
3 $\beta$ -acetate.

To a solution of 10 $\alpha$ -cholesta-5,7-dien-3 $\beta$ -acetate (83c) (302 mg) in dichloromethane (25 ml) was added 4-phenyl-1,2,4-triazoline-3,5-

dione (110) (121 mg) in dichloromethane (20 ml) and the mixture stirred at room temperature under nitrogen in the dark overnight. Evaporation of the solvent gave a residue which was dissolved in ether-pentane and filtered to remove the solid material. Evaporation of the solvent gave the 3 $\beta$ -acetoxy-10 $\alpha$ -cholest-6-ene-5 $\alpha$ ,8 $\alpha$ -cycloadduct (117) (400 mg) as a gum,  $\nu_{\text{max}}$ . 1780, 1738, 1712, 1605, 1508  $\text{cm}^{-1}$ . N.m.r.  $\delta$  7.47 ( $W_{\frac{h}{2}}$  8Hz; C(4')-phenyl), 6.83, 6.67, 6.47, 6.33 (AB pattern,  $\delta_A$  6.75,  $\delta_B$  6.42,  $J_{AB}$  = 8Hz; C(6)H, C(7)H, 5.32 ( $W_{\frac{h}{2}}$  8Hz; C(3)H, 1.05 (OAc), 1.22 (C(19)H<sub>3</sub>), 0.90 (C(18)H<sub>3</sub>) ppm. m/e 426, 424, 366, 364 (100%) 177. (Found: ( $M^+$ -77) 424.3334.  $\text{C}_{37}\text{H}_{51}\text{N}_3\text{O}_4$  requires  $M^+$  601, ( $M^+$ - $\text{C}_8\text{H}_7\text{O}_2\text{N}_3$ ) 424.3341.)



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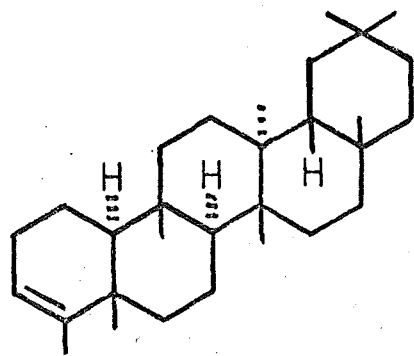
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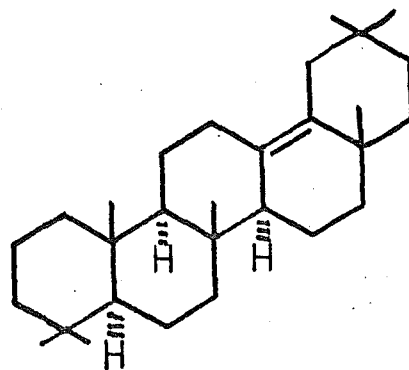
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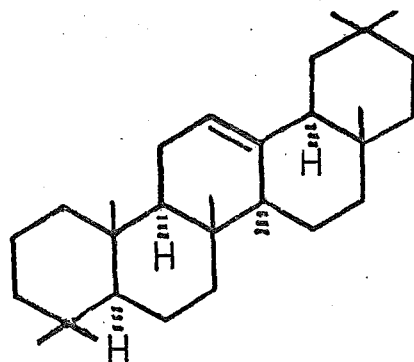
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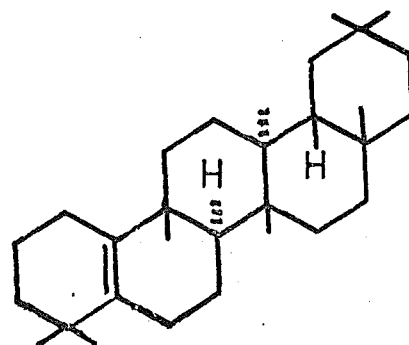
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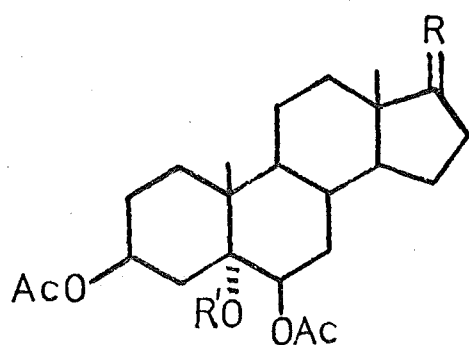
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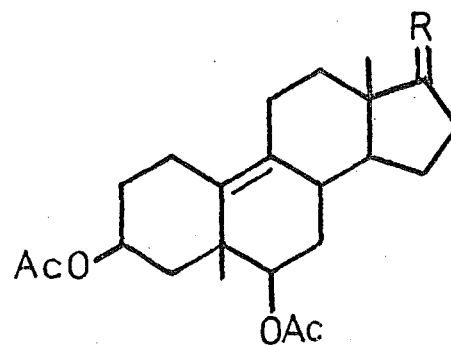
(3)



(4)



(5)



(6)

(a)  $R = \beta\text{C}_8\text{H}_{17}, \alpha\text{H}; R' = \text{H}$

(b)  $R = \beta\text{H}, \alpha\text{H}; R' = \text{H}.$

(c)  $R = \text{O}; R' = \text{H}.$

(d)  $R = \beta\text{CH}_3\text{CO}, \alpha\text{H}; R' = \text{H}$

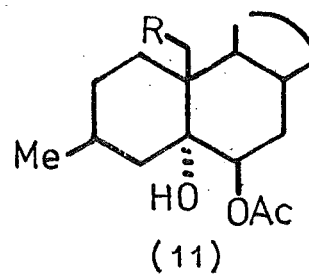
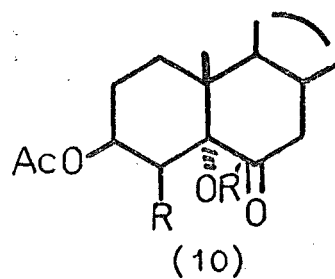
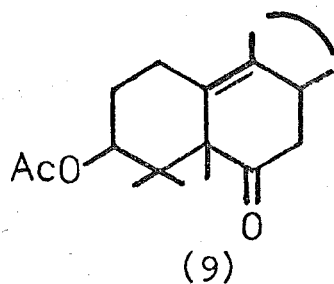
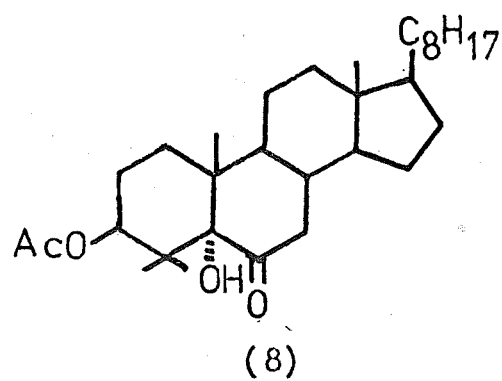
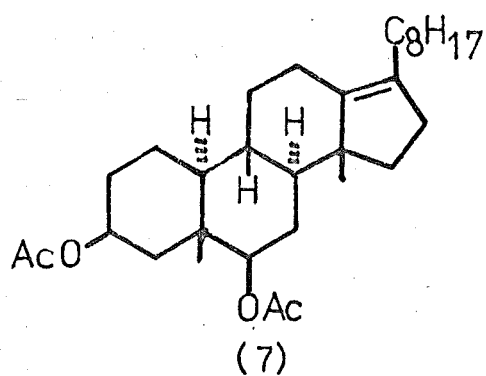
(e)  $R = \beta\text{C}_8\text{H}_{17}, \alpha\text{H}; R' = \text{Ac}$

(a)  $R = \beta\text{C}_8\text{H}_{17}, \alpha\text{H}.$

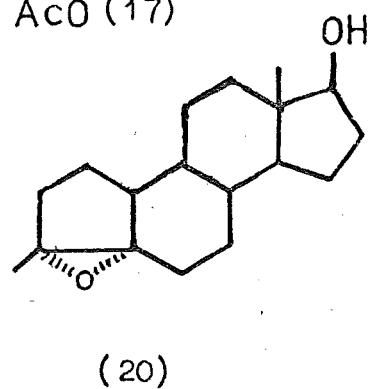
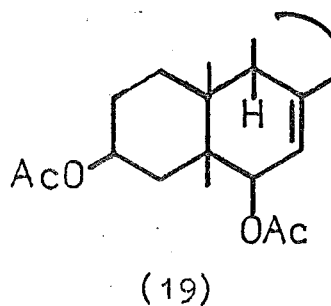
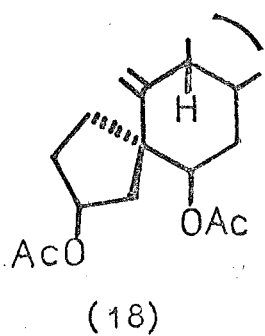
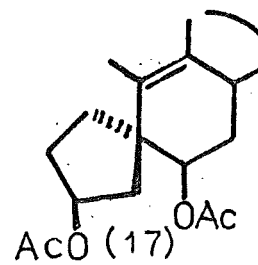
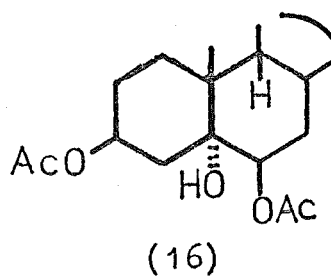
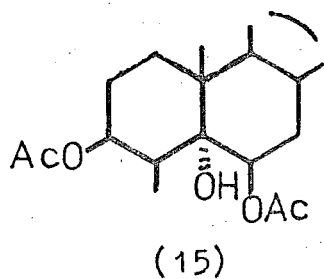
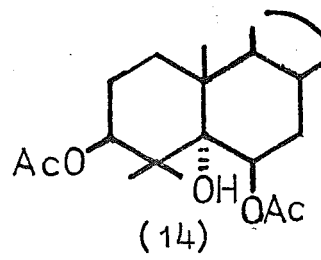
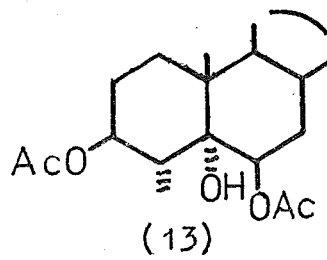
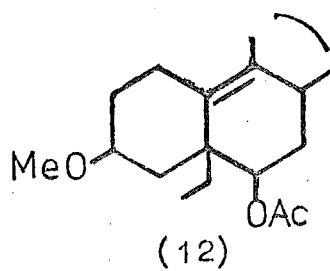
(b)  $R = \beta\text{H}, \alpha\text{H}.$

(c)  $R = \text{O}.$

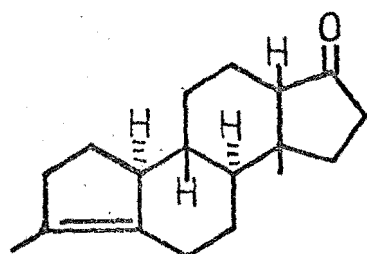
(d)  $R = \beta\text{CH}_3\text{CO}, \alpha\text{H}.$



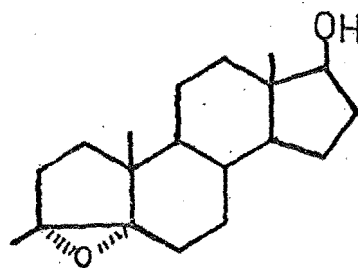
- (a)  $R = H, R' = H.$       (a)  $R = CH_3.$   
 (b)  $R = Ac, R' = H.$       (b)  $R = H.$   
 (c)  $R = H, R' = CH_3$



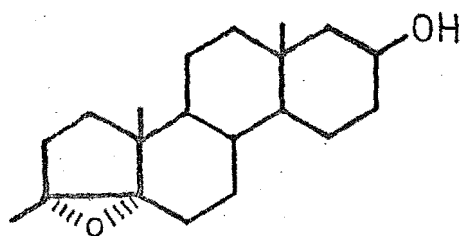




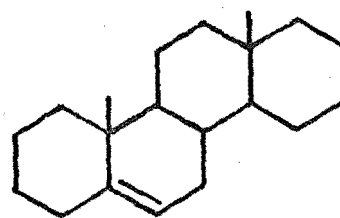
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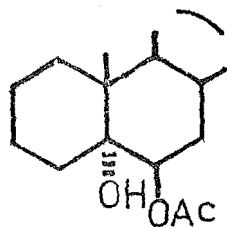
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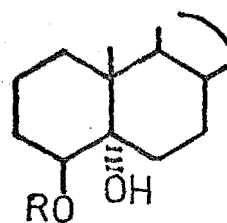
(23)



(24)



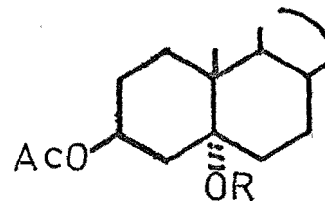
(25)



(26)

(a)  $R = H.$

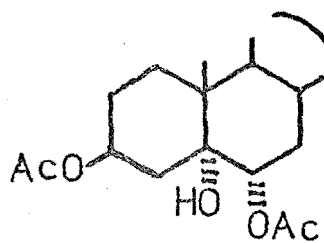
(b)  $R = Ac.$



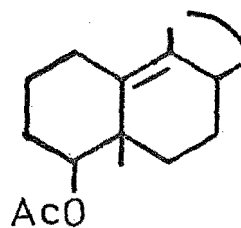
(27)

(a)  $R = H.$

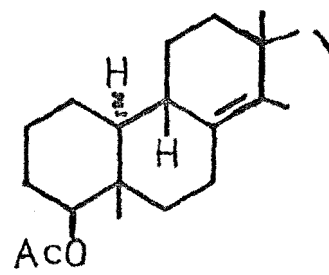
(b)  $R = Ac.$



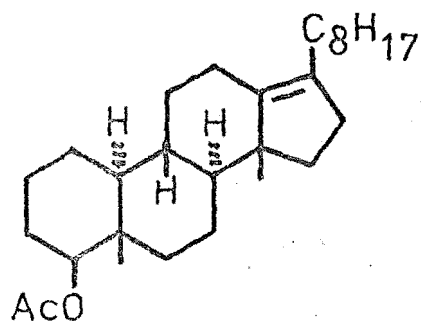
(28)



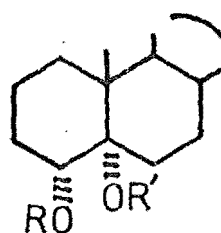
(29)



(30)



(31)

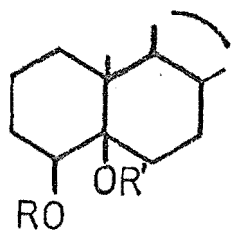


(32)

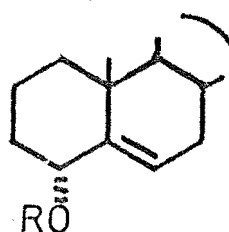
(a)  $R = H; R' = H.$

(b)  $R = Ac; R' = H.$

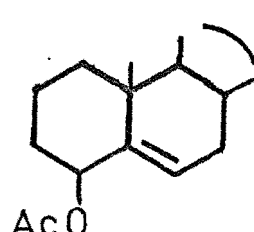
(c)  $R = Ac; R' = Ac.$



(33)

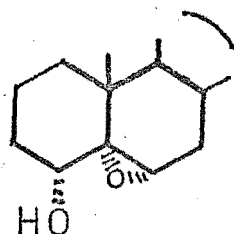


(34)

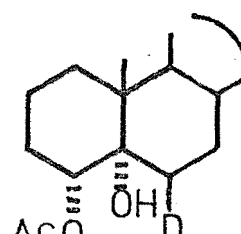


(35)

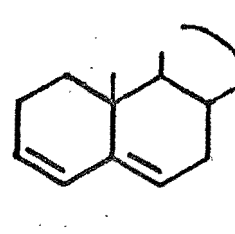
- (a)  $R = H$ ;  $R' = H$ . (a)  $R = H$ .  
 (b)  $R = Ac$ ;  $R' = H$ . (b)  $R = Ac$ .  
 (c)  $R = Ac$ ;  $R' = Ac$ .



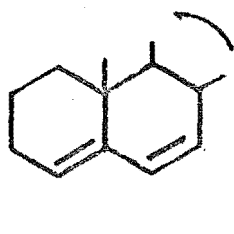
(36)



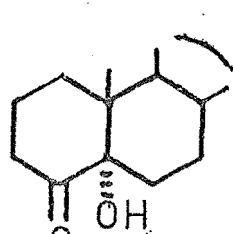
(37)



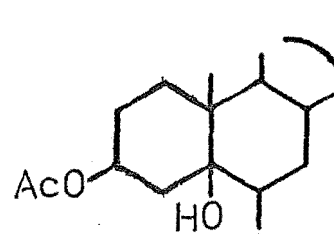
(38)



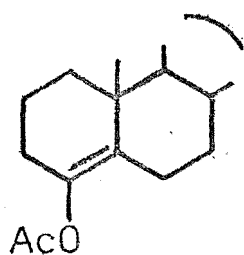
(39)



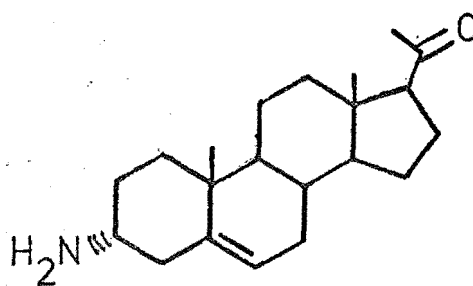
(40)



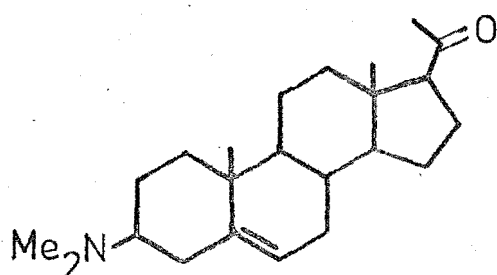
(41)



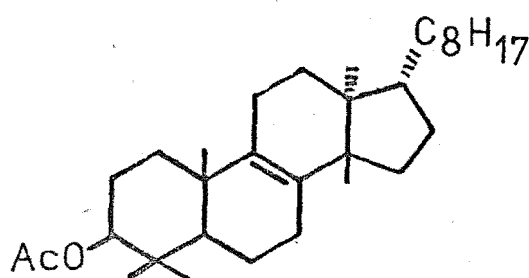
(42)



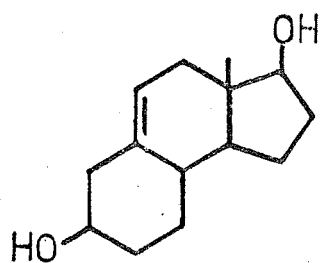
(43)



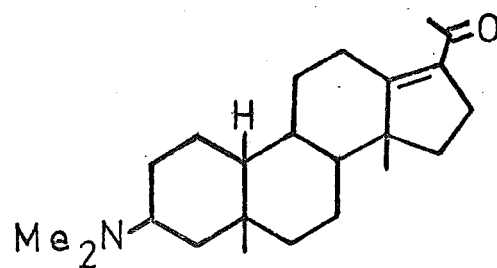
(44)



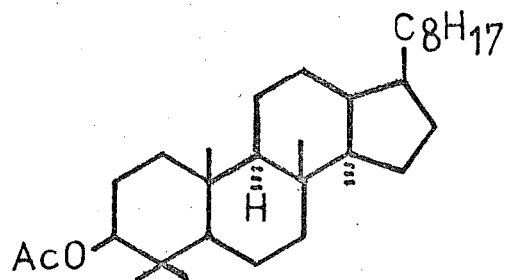
(45)



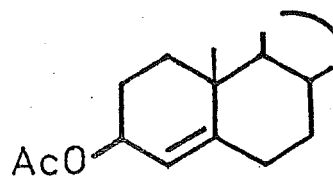
(46)



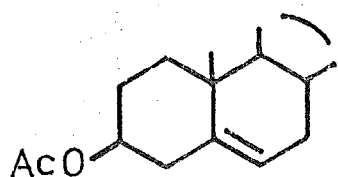
(47)



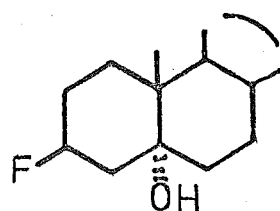
(48)



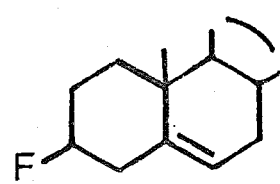
(49)



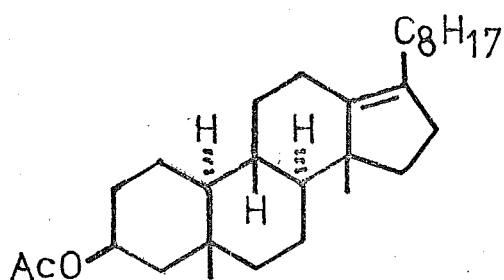
(50)



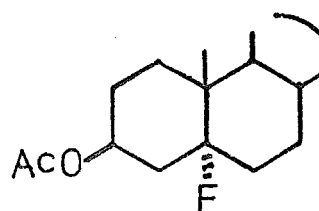
(51)



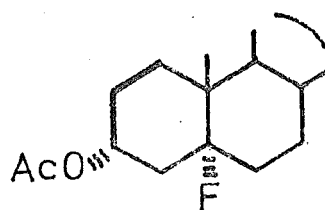
(52)



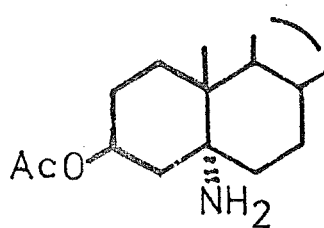
(53)



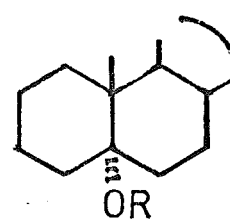
(54)



(55)



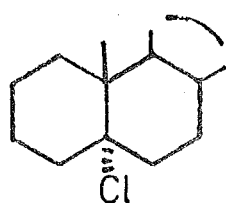
(56)



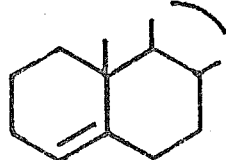
(57)

(a) R = H.

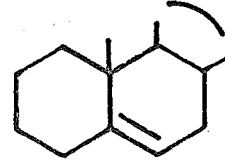
(b) R = Ac.



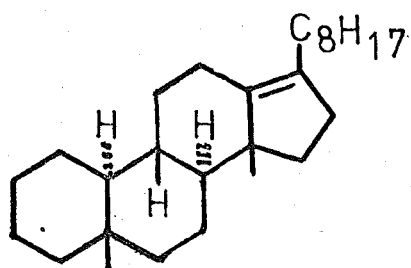
(58)



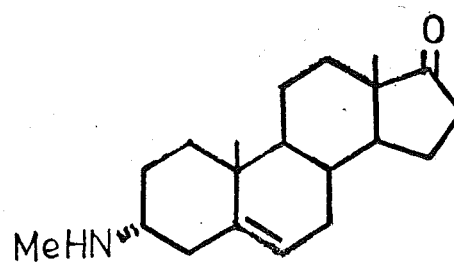
(59)



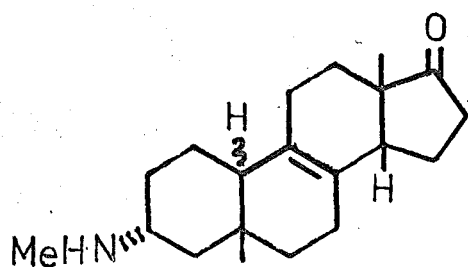
(60)



(61)



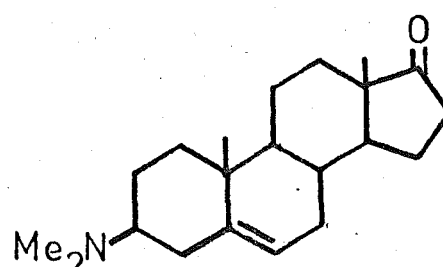
(62)



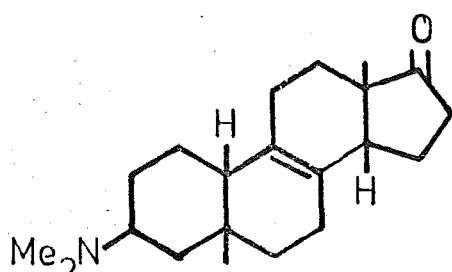
(63)

(a) 10 $\alpha$ H

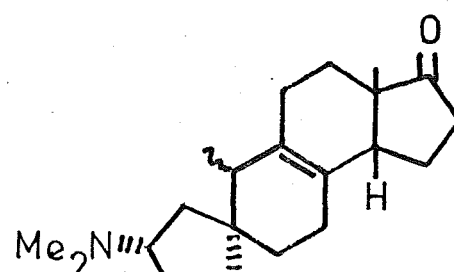
(b) 10 $\beta$ H



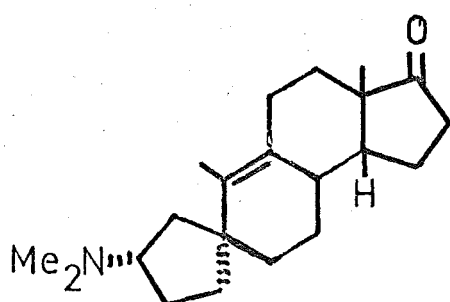
(64)



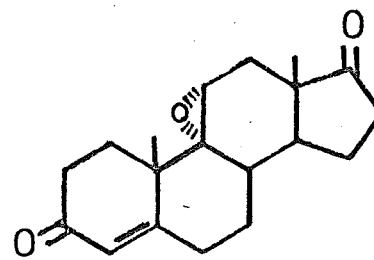
(65)



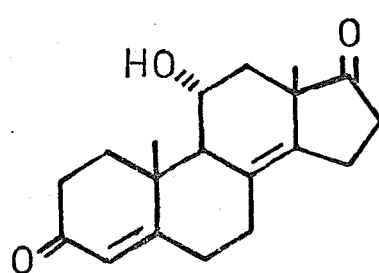
(66)



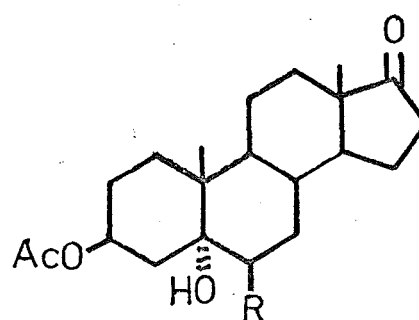
(67)



(68)



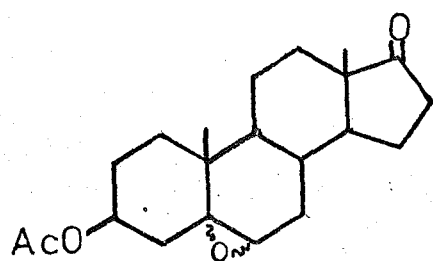
(69)



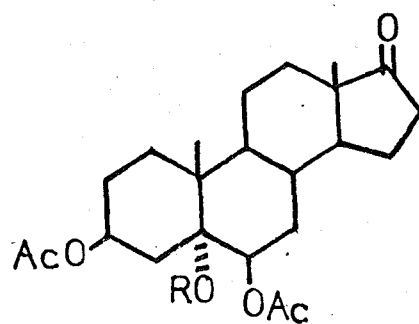
(70)

(a) R = Cl

(b) R = F



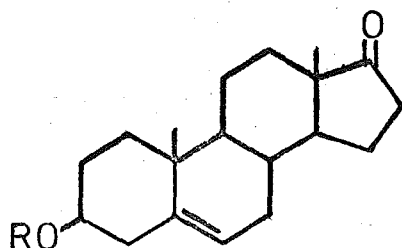
(71)



(72)

(a) R = H

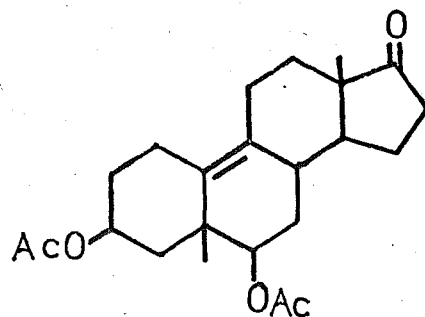
(b) R = Ac



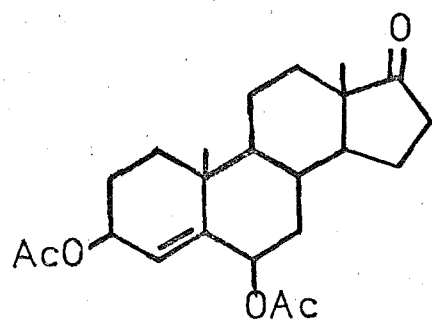
(73)

(a) R = H

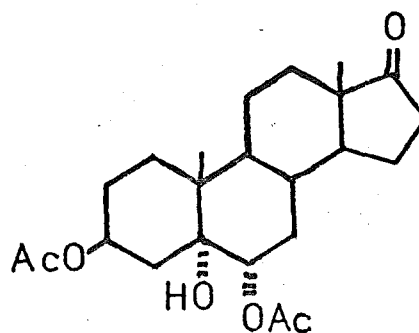
(b) R = Ac



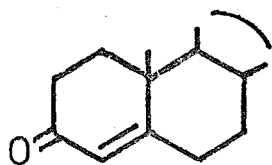
(74)



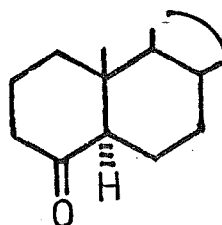
(75)



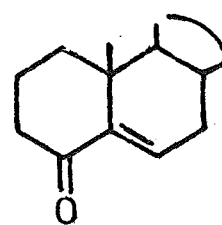
(76)



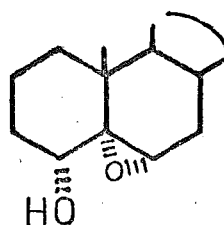
(77)



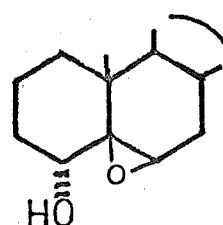
(78)



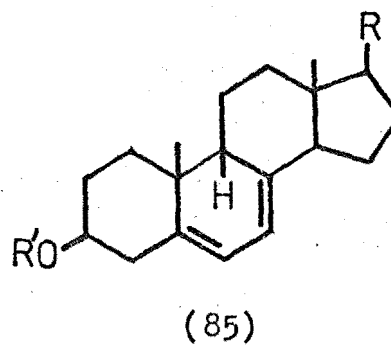
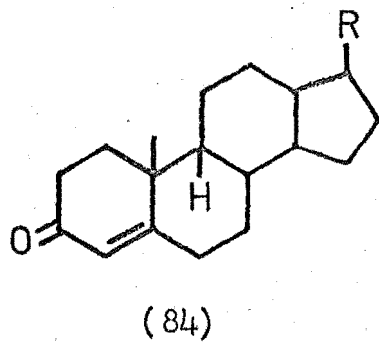
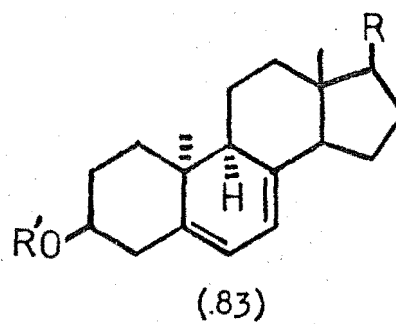
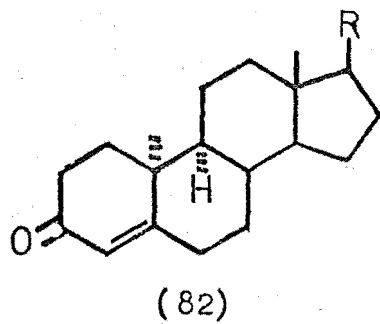
(79)



(80)



(81)

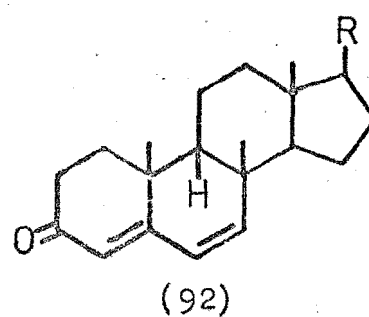
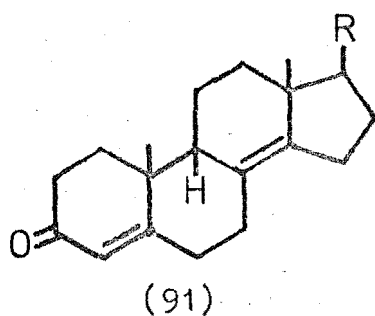
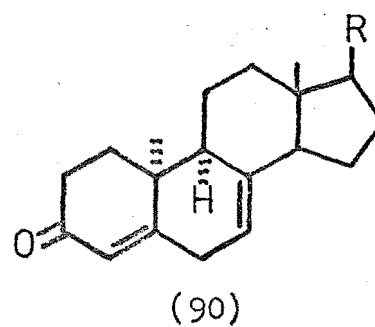
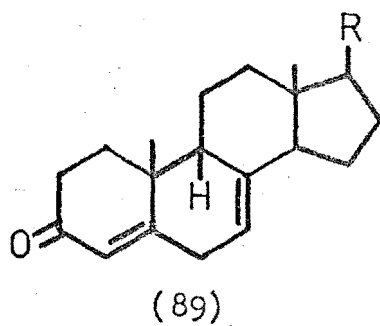
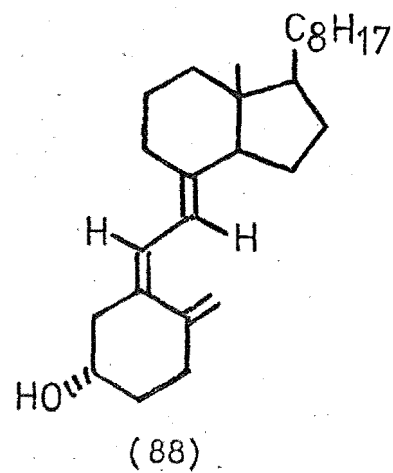
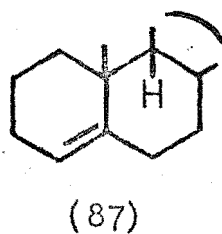
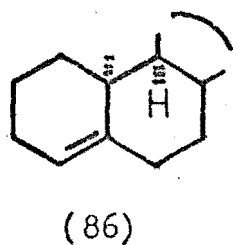


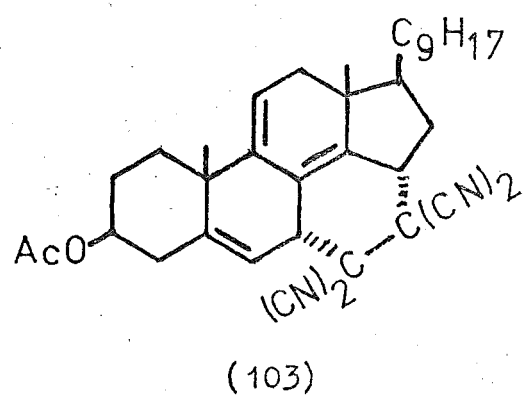
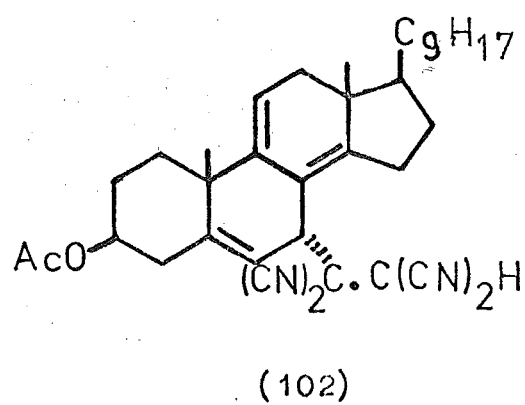
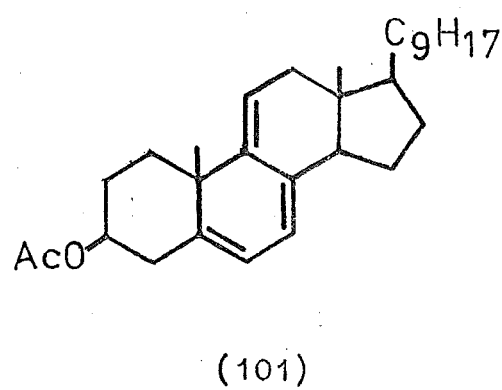
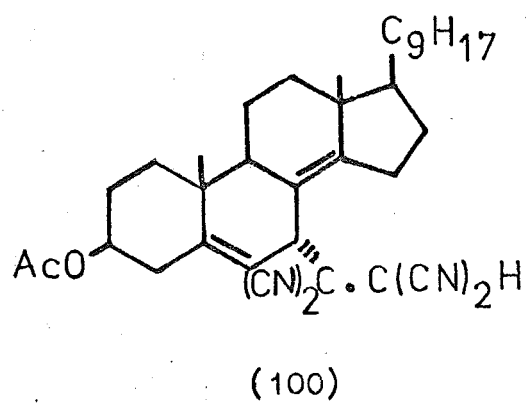
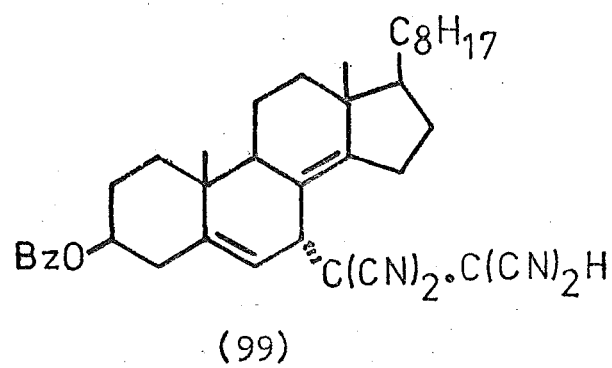
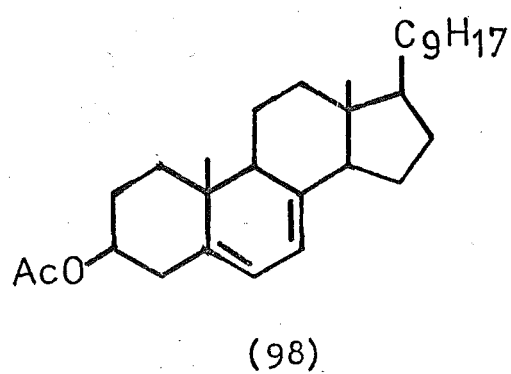
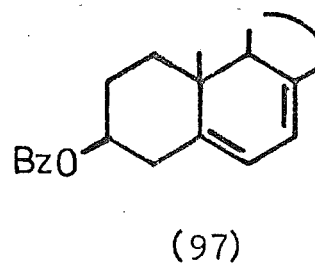
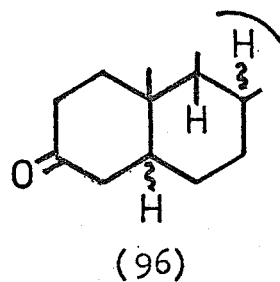
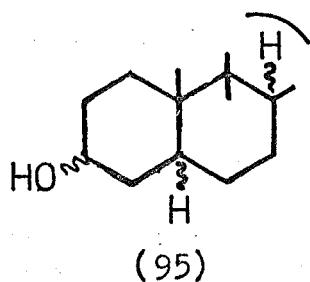
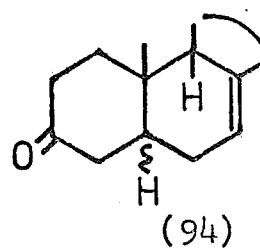
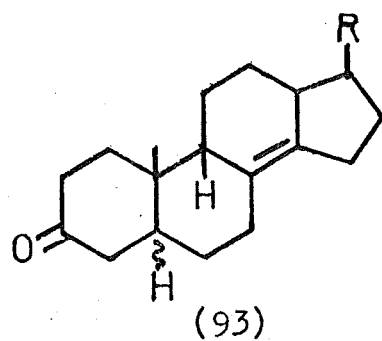
(a)  $R = C_9H_{17}$ ;  $R' = H$ .

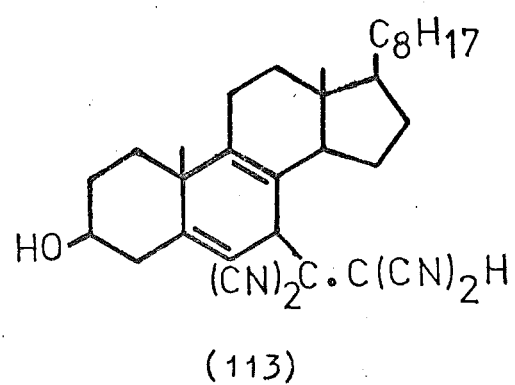
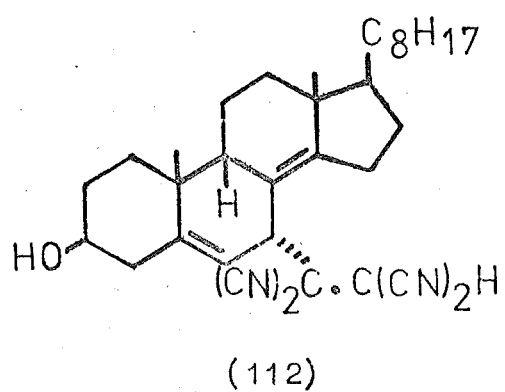
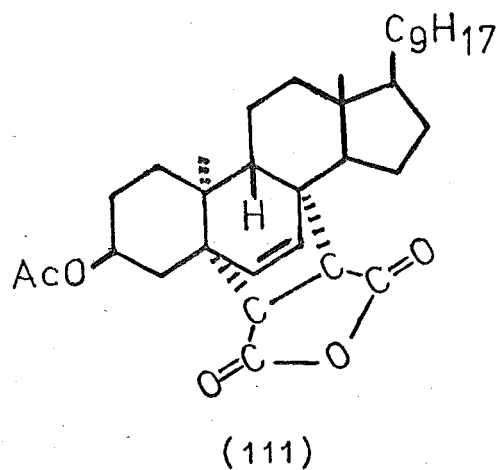
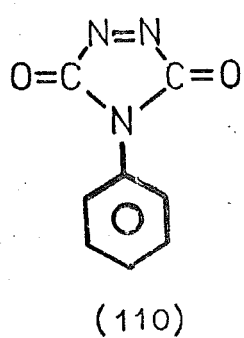
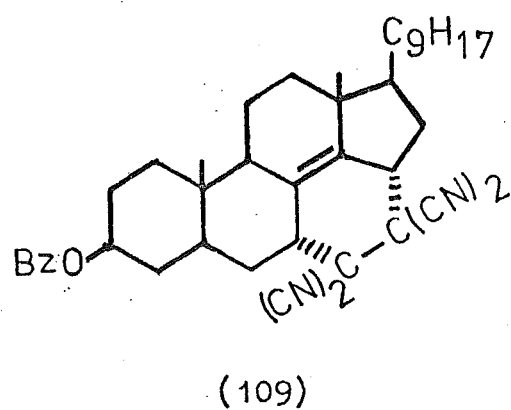
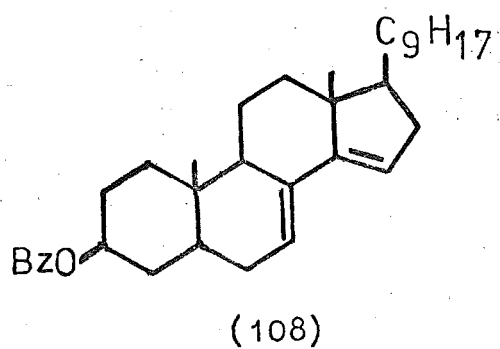
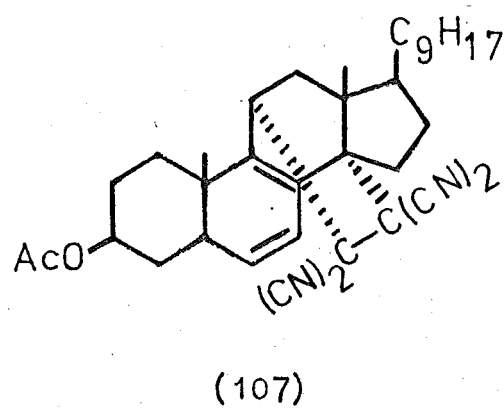
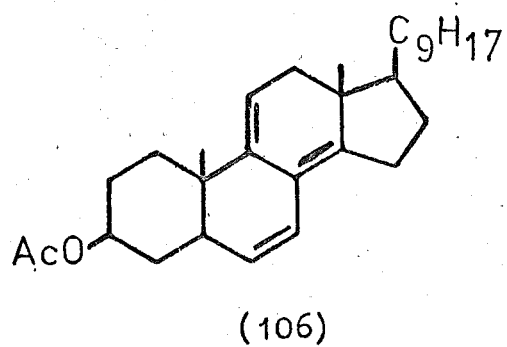
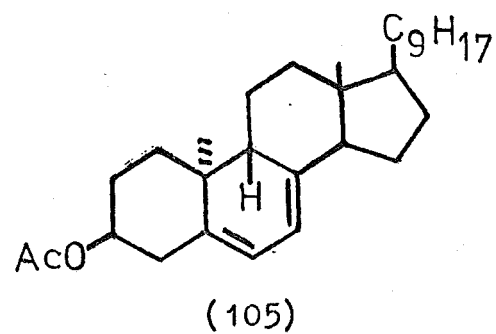
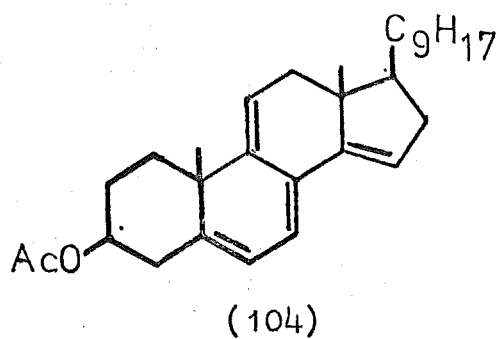
(b)  $R = C_8H_{17}$ ;  $R' = H$ .

(c)  $R = C_8H_{17}$ ;  $R' = Ac$ .

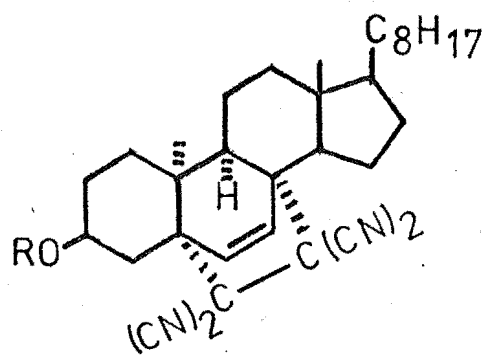
(d)  $R = C_8H_{17}$ ;  $R' = Bz$ .



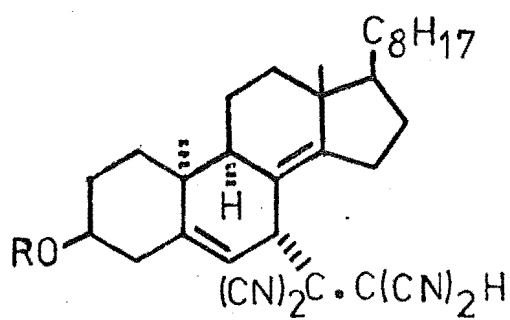








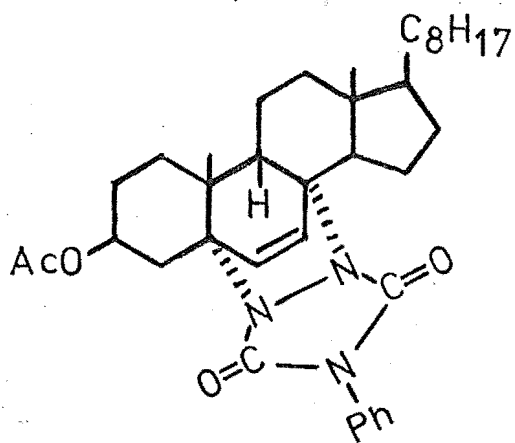
(114)



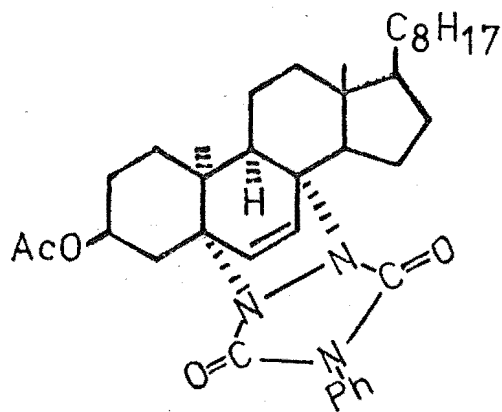
(115)

(a) R = H.

(b) R = Bz.



(116)



(117)